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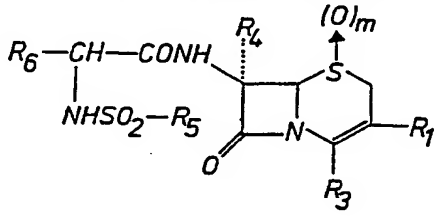
# (54) 7β-Acylamido-3-cephem-4-carboxylic acid compounds, processes for the manufacture thereof, pharmaceutical preparations containing these compounds, and the use of the latter

(57) 7β-Acylamido-3-cephem-4-carboxylic acid compounds of the formula



(I)

in which

m is 0, 1 or 2,

$R_1$ represents hydrogen, lower alkyl, lower alkenyl, lower alkoxy, halogen, a group of the formula $—CH_2—R_2$, wherein $R_2$ represents a free, esterified or etherified hydroxy or mercapto group or an ammonio group, or a group of the formula $—CH=CHR_2$ wherein $R_2$ is an etherified mercapto group,

$R_3$ represents carboxy or protected carboxy,

$R_4$ represents hydrogen,

$R_5$ represents an organic radical that is bonded by a carbon atom to the sulphonyl group, and

$R_6$ represents a heterocyclic radical,

and hydrates and salts of these compounds exhibit antibiotic properties and are effective against gram-positive and gram-negative micro-organisms. The novel compounds can be used, for example, in the form of antibiotically active preparations for the treatment of infections.

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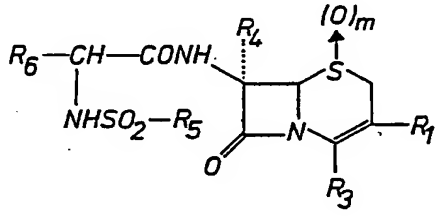
The chemical formulae appearing in the printed specification were submitted after the data of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

**7β-acylamido-3-cephem-4-carboxylic acid compounds, processes for the manufacture thereof, pharmaceutical preparations containing these compounds, and the use of the latter**

The present invention relates to novel 7β-acylamido-3-cephem-4-carboxylic acid compounds, to processes for the manufacture thereof, to pharmaceutical preparations containing such compounds, and to their use for the manufacture of pharmaceutical preparations or as pharmacologically active compounds, and to novel intermediates and processes for their manufacture.

The present invention relates to 7β-acylamido-3-cephem-4-carboxylic acid compounds of the formula



(I)

in which

*m* represents an integer from 0 to 2,

$R_1$ represents hydrogen, lower alkyl, lower alkenyl, lower alkoxy, halogen, a group of the formula $—CH_2—R_2$ wherein $R_2$ represents a free, esterified or etherified hydroxy or mercapto group or an ammonio group, or a group of the formula $—CH=CHR_2$ wherein $R_2$ represents an etherified mercapto group,

$R_3$ represents carboxy or protected carboxy,

$R_4$ represents hydrogen,

$R_5$ represents an organic radical that is bonded by a carbon atom to the sulphonyl group, and

$R_6$ represents a heterocyclic radical,

and to stereoisomers, mixtures of these stereoisomers, hydrates and salts of compounds of the formula I, to processes for the manufacture of compounds of the formula I, to pharmaceutical preparations that contain compounds of the formula I and to the use of compounds of the formula I for the manufacture of pharmaceutical preparations or as pharmacologically active compounds.

In the description of the present invention, the term "lower" used in connection with groups or radicals, for example lower alkyl, lower alkylene, lower alkoxy, lower alkanoyl *etc.*, means that, unless expressly defined otherwise, the groups or radicals so designated contain up to 7, and preferably up to 4, carbon atoms.

In the formula I, *m* represents especially 0. If *m* represents 1, the 1-oxido group can be in the α- or β-orientation. It is also possible for there to be a mixture of compounds of the formula I having the 1-oxido group in both orientations.

The carbon atom having the substituted amino group of the partial formula $—NHSO_2—R_5$ has the R— or S— configuration. It is also possible for there to be a mixture of compounds of the formula I having the substituted amino group of the partial formula $—NHSO_2—R_5$ in both configurations.

Lower alkyl $R_1$ may contain from 1 to 4 carbon atoms and is, for example, ethyl, propyl, butyl or, especially, methyl.

Lower alkenyl $R_1$ may contain from 1 to 4 carbon atoms and is, for example, vinyl or allyl.

Lower alkoxy $R_1$ may contain from 1 to 4 carbon atoms and is, for example, ethoxy, propoxy, butoxy or, especially, methoxy.

Halogen $R_1$ is fluorine, bromine, iodine or, preferably, chlorine.

Esterified hydroxy or mercapto $R_2$ may be a hydroxy or mercapto group that is esterified by an aliphatic carboxylic acid, by an aliphatic carboxylic acid substituted by acyl, for example lower alkanoyl, for example acetyl, by carbamic acid or by a substituted carbamic acid, for example lower alkanoyloxy, for example acetoxy, lower alkanoyl-lower alkanoyloxy, for example acetoacetoxy, or carbamoyloxy or lower alkanoylthio, for example acetylthio or formylthio, or carbamoylthio.

Substituents of carbamic acid are, for example, lower alkyl, for example methyl or ethyl, or lower alkyl substituted by halogen, for example chlorine, or by lower alkanoyloxy, for example acetoxy, for example 2-chloroethyl or 2-acetoxyethyl.

Hydroxy or mercapto $R_2$ esterified by a substituted carbamic acid is, for example, methylcarbamoyloxy, ethylcarbamoyloxy, 2-chloroethylcarbamoyloxy, 2-acetoxyethylcarbamoyloxy or methylcarbamoylthio.

Etherified hydroxy or mercapto $R_2$ may be a hydroxy or mercapto group that is etherified by an aliphatic hydrocarbon radical, for example lower alkoxy having from 1 to 4 carbon atoms, for example methoxy or ethoxy, or lower alkylthio having from 1 to 4 carbon atoms, for example, methylthio.

Etherified mercapto $R_2$ is preferably etherified by a heterocycle that is bonded *via* a ring carbon atom to the mercapto group, for example by a monocyclic heterocyclic that contains from 1 to 4 nitrogen hetero atoms and optionally also an oxygen or sulphur atom, or by a bicyclic heterocycle having from 1 to 5 nitrogen hetero atoms. An etherified mercapto group of this type is termed a "heterocyclylthio group $R_2$" in the following.

In a heterocyclylthio group $R_2$, heterocyclyl is especially aromatic, monocyclic, five- or six-membered diaza-, triaza-, tetraaza-, thiaza-, thidiaza-, thia-, oxaza- or oxadiaza-cyclyl, or is aromatic or partially saturated, bicyclic aza-, diaza-, triaza-, tetraaza- or pentaaza-bicyclyl containing five or six ring atoms per ring.

Substituents of the mentioned heterocyclyl radical in a heterocyclylthio group $R_2$ are, for example, unsubstituted lower alkyl, for example ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert.-butyl, especially methyl, or substituted lower alkyl, for example methyl or ethyl, which is substituted by the following functional, modified functional and heterocyclic groups: hydroxy, esterified hydroxy, for example lower alkanoyloxy, for example acetoxy, or halogen, for example fluorine or chlorine, lower alkylphosphonyl optionally present in salt form, for example in the form of an alkali metal salt, for example a sodium salt, for example sodium methylphosphonyl or sodium ethylphosphonyl, di-lower alkylphosphonyl, for example dimethylphosphonyl or diethylphosphonyl, carboxy, sulpho, carboxy or sulpho present in salt form, for example in the form of an alkali metal or ammonium salt, for example a sodium salt, for example sodium carboxylate or sodium sulphonate, esterified carboxy, for example lower alkoxycarbonyl, for example ethoxycarbonyl, sulphamino, sulphamino present in salt form, for example in the form of an alkali metal salt, for example a sodium salt, for example sodium sulphonatoamino, sulphamoyl, amino, lower alkylamino, for example methylamino or ethylamino, di-lower alkylamino, for example dimethylamino or diethylamino, acylamino, for example lower alkanoylamino, for example acetylamino, or lower alkanoylamino substituted by carboxy or halogen, for example chlorine, for example carboxyacetylamino or chloroacetylamino, and tetrazolyl, for example tetrazol-1H-5-yl.

A lower alkyl radical substituted by these groups is, for example: hydroxy-lower alkyl, for example hydroxymethyl or 2-hydroxyethyl, acetoxy-lower alkyl, for example acetoxymethyl or 2-acetoxyethyl, halo-lower alkyl, for example chloromethyl, 2-chloroethyl, 2,2,2-trichloroethyl or trifluoromethyl, lower alkylphosphono-lower alkyl, for example ethylphosphonomethyl, di-lower alkylphosphono-lower alkyl, for example diethylphosphonomethyl, carboxy-lower alkyl, for example carboxymethyl or 2-carboxyethyl, sulpho-lower alkyl, for example sulphomethyl or 2-sulphoethyl, lower alkoxycarbonyl-lower alkyl, for example ethoxycarbonylmethyl or 2-ethoxycarbonylethyl, sulphamoyl-lower alkyl, for example sulphamoylmethyl or 2-sulphamoylethyl, sodium sulphonatoamino-lower alkyl, for example sodium sulphonatoaminomethyl or 2-sodium sulphonatoaminoethyl, amino-lower alkyl, for example aminomethyl or 2-aminoethyl, lower alkylamino-lower alkyl, for example methylaminomethyl or 2-methylaminoethyl, di-lower alkylamino-lower alkyl, for example dimethylaminomethyl or 2-dimethylaminoethyl, lower alkanoylamino-lower alkyl, for example 2-acetylaminoethyl, carboxy-lower alkanoylamino-lower alkyl, for example 3-carboxypropionylaminoethyl or 2-carboxyacetylaminoethyl, or halo-lower alkanoylamino-lower alkyl, for example 3-chloropropionylaminoethyl or 2-chloroacetylaminoethyl, and tetrazolyl-lower alkyl, for example tetrazol-1H-5-ylmethyl or 2-(tetrazol-1H-5-yl)-ethyl.

Lower alkenyl, for example vinyl or allyl, functional groups or modified, for example protected, functional groups, for example halogen, for example fluorine, chlorine or bromine, amino or substituted amino, for example amino mono- or di-substituted, for example, by lower alkyl, for example methyl or ethyl, for example methylamino or dimethylamino, acylamino, for example lower alkanoylamino, for example acetylamino, or lower alkylsulphonylamino, for example mesylamino, or lower alkanoylamino substituted by halogen, for example chlorine, or by carboxy, for example 3-chloropropionylamino or 3-carboxypropionylamino, nitro, hydroxy, lower alkoxy, for example methoxy or ethoxy, carboxy, esterified carboxy, for example lower alkoxycarbonyl, for example methoxycarbonyl or ethoxycarbonyl, amidated carbonyl, for example carbamoyl, mono- or di-lower alkylated carbamoyl, for example methylcarbamoyl or dimethylcarbamoyl, or cyano, and oxo or oxido; are also possible substituents of the heterocyclyl radical in a heterocyclylthio group $R_2$.

A heterocyclylthio group $R_2$ in which heterocyclyl is aromatic, monocyclic, five-membered heterocyclyl is preferably imidazolylthio, for example 2-imidazolylthio, triazolylthio, or triazolylthio substituted by lower alkyl, for example methyl, and/or by phenyl, for example 1H-1,2,3-triazol-5-ylthio, 1-methyl-1H-1,2,3-triazol-4-ylthio, 1H-1,2,4-triazol-3-ylthio, 5-methyl-1H-1,2,4-triazol-4-ylthio, 1H-1,2,4-triazol-3-ylthio, 5-methyl-1H-1,2,4-triazol-3-ylthio or 4,5-dimethyl-1,2,4-triazol-3-ylthio, tetrazolylthio, for example 1H-tetrazol-5-ylthio, or tetrazolylthio substituted by lower alkyl, for example methyl or ethyl, or by substituted lower alkyl, for example ethyl- or diethyl-phosphonomethyl, 2-carboxyethyl, sulphomethyl, 2-sulphoethyl, 2-sodium sulphonatoethyl, 2-dimethylaminoethyl, cyanomethyl or tetrazolylmethyl, for example 1-methyl-1H-tetrazol-5-ylthio, 1-ethyl- or 1-diethylphosphonylmethyl-1H-tetrazol-5-ylthio, 1-carboxymethyl-1H-tetrazol-5-ylthio, 1-(2-carboxyethyl)-1H-tetrazol-5-ylthio, 1-sulphomethyl-1H-tetrazol-5-ylthio, 1-(2-sulphoethyl)-1H-tetrazol-5-ylthio, 1-(2-sodium sulphonatoethyl)-1H-tetrazol-5-ylthio, 1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthio, 1-

cyanomethyl-1H-tetrazol-5-ylthio, 1-(tetrazol-1H-5-ylmethyl)-1H-tetrazol-5-ylthio, thiazolylthio, or thiazolylthio substituted by carboxy-lower alkyl, for example carboxymethyl, and/or by lower alkyl, for example methyl, for example 2-thiazolylthio, 4-methyl-5-carboxymethylthiazol-2-ylthio or 4,5-dimethyl-2-thiazolylthio, isothiazolylthio, for example 3-isothiazolylthio, 4-isothiazolylthio or 5-isothiazolylthio, thiadiazolylthio, or thiadiazolylthio substituted by lower alkyl, for example methyl, for example 1,2,3-thiadiazol-4-ylthio, 1,2,3-thiadiazol-5-ylthio, 1,3,4-thiadiazol-2-ylthio, 2-methyl-1,3,4-thiadiazol-5-ylthio, 1,2,4-thiadiazol-5-ylthio or 1,2,5-thiadiazol-3-ylthio, thiatriazolylthio, for example 1,2,3,4-thiatriazol-5-ylthio, oxazolylthio, or oxazolylthio substituted by lower alkyl, for example methyl, for example 2- or 5-oxazolylthio, or 4-methyl-5-oxazolylthio, isoxazolylthio substituted by lower alkyl, for example methyl, for example 3-methyl-5-isoxazolylthio, oxadiazolylthio, or oxadiazolylthio substituted by lower alkyl, for example methyl, for example 1,2,4-oxadiazol-5-ylthio or 2-methyl-1,3,4-oxadiazol-5-ylthio.

A heterocyclylthio group $R_2$ in which heterocyclyl is aromatic, monocyclic, six-membered heterocyclyl and contains from 1 to 3 nitrogen atoms is preferably 5,6-dioxotetrahydro-as-triazinylthio, or 5,6-dioxotetrahydro-as-triazinylthio substituted by lower alkyl, for example methyl, carboxy-lower alkyl, for example carboxymethyl, or by sulpho-lower alkyl, for example sulphomethyl, for example 1- or 2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio, 4-methyl-5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio, 1- or 2-carboxymethyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio, 4-carboxymethyl-5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio, 1- or 2-sulphomethyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio or 4-sulphomethyl-5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio.

A heterocyclylthio group $R_2$ in which heterocyclyl is aromatic or partially saturated, bicyclic heterocyclyl containing five or six ring atoms per ring is preferably indolylthio, indolylthio substituted by lower alkyl, for example methyl, for example indol-2-ylthio or N-methylindol-2-ylthio, isoindolylthio, for example isoindol-2-ylthio, quinolylthio, for example 2-, 4- or 8-quinolylthio, benzimidazolylthio, benzimidazolylthio substituted by lower alkyl, for example methyl, or by carboxy-lower alkyl, for example carboxymethyl, for example 1-methyl-, 1-carboxymethyl- or 1-(2-carboxyethyl)-benzimidazol-2-ylthio, benzotriazolylthio, benzotriazolylthio substituted by lower alkyl, for example methyl, or by carboxy-lower alkyl, for example carboxymethyl, for example 1-methyl- or 1-carboxymethyl-1H-benzo[d]triazol-5-ylthio, tetrazolopyridazinylthio, or tetrazolopyridazinylthio substituted by lower alkyl, for example methyl or ethyl, carboxy, carboxy-lower alkyl, for example carboxymethyl, carbamoyl, lower alkylcarbamoyl, for example methylcarbamoyl, di-lower alkylcarbamoyl, for example dimethylcarbamoyl, amino, lower alkylamino, for example methylamino, or by di-lower alkylamino, for example dimethylamino or diethylamino, for example 8-methyl-, 8-ethyl-, 8-carboxy-, 8-carboxymethyl-, 8-(2-carboxyethyl)-, 8-carbamoyl-, 8-methylcarbamoyl-, 8-dimethylcarbamoyl-, 8-amino-, 8-dimethylamino- or 8-diethylamino-tetrazolo[1,5-b]pyridazin-6ylthio.

An ammonio group $R_2$ is derived from an organic tertiary nitrogen-containing base, for example from a tertiary aliphatic amine or preferably from a tertiary heterocyclic aromatic nitrogen base, the base in question being bonded by its nitrogen atom to the methylene group in the 3-position of the cephem nucleus. The positive charge at the quaternary nitrogen atom of the ammonio group is compensated for, for example, by the negatively charged carboxylate group which is in the 4-position of the cephem nucleus in place of the undissociated carboxy group.

An ammonio group $R_2$ that is derived from a tertiary aliphatic amine is, for example, tri-lower alkylammonio, for example trimethyl- or triethylammonio.

A quaternary ammonio group $R_2$ that is derived from a tertiary heterocyclic aromatic nitrogen base is, for example, 1-pyrazolio, or 1-pyrazolio substituted in the 2-position by lower alkyl, for example methyl or ethyl, lower alkenyl, for example vinyl or allyl, carboxy-lower alkyl, for example carboxymethyl, lower alkoxycarbonyl-lower alkyl, for example methoxycarbonylmethyl, sulpho-lower alkyl, for example sulphomethyl, amino-lower alkyl, for example 2-aminoethyl, or by di-lower alkylamino-lower alkyl, for example 2-dimethylaminoethyl, for example 2-methyl- or 2-ethyl-1-pyrazolio, 2-allyl- or 2-vinyl-1-pyrazolio, 2-sulphomethyl-1-pyrazolio, 2-(2-aminoethyl)-1-pyrazolio or 2-(2-dimethylaminoethyl)-1-pyrazolio, 1-triazolio, or 1-triazolio substituted in the 3-position by lower alkyl, for example methyl or ethyl, carboxy-lower alkyl, for example carboxymethyl, or by di-lower alkylamino-lower alkyl, for example 2-dimethylamino-ethyl, for example 3-methyl-1-triazolio, 3-carboxymethyl-1-triazolio or 3-(2-dimethylaminoethyl)-1-triazolio.

An ammonio group $R_2$ that is derived from a tertiary heterocyclic aromatic nitrogen base is preferably pyridinio, or pyridinio mono- or di-substituted by lower alkyl, for example methyl, carbamoyl, lower alkylcarbamoyl, for example methylcarbamoyl, hydroxy-lower alkyl, for example hydroxymethyl, lower alkoxy-lower alkyl, for example methoxymethyl, cyano-lower alkyl, for example cyanomethyl, carboxy-lower alkyl, for example carboxymethyl, sulpho-lower alkyl, for example 2-sulphoethyl, carboxy-lower alkenyl, for example 2-carboxyvinyl, carboxy-lower alkylthio, for example carboxymethylthio, thiocarbamoyl, halogen, for example bromine or chlorine, carboxy, sulpho, or by cyano, for example lower alkylpyridinio, for example 2-, 3- or 4-methylpyridinio or 2-, 3- or 4-ethylpyridinio, carbamoylpyridinio, for example 3- or 4-carbamoylpyridinio, lower alkylcarbamoylpyridinio, for example 3- or 4-methylcarbamoylpyridinio, di-lower

alkylcarbamoylpyridinio, for example 3- or 4-dimethylcarbamoylpyridinio, hydroxy-lower alkylpyridinio, for example 3- or 4-hydroxymethylpyridinio, lower alkoxy-lower alkylpyridinio, for example 4-methoxymethylpyridinio, cyano-lower alkylpyridinio, for example 3-cyanomethylpyridinio, carboxy-lower alkylpyridinio, for example 3-carboxymethylpyridinio, sulpho-lower alkylpyridinio, for example 4-(2-sulphoethyl)-pyridinio, carboxy-lower alkenylpyridinio, for example 3-(2-carboxyvinyl)-pyridinio, carboxy-lower alkylthiopyridinio, for example 4-carboxymethylthiopyridinio, thiocarbamoylpyridinio, for example 4-thiocarbamoylpyridinio, halopyridinio, for example 3-bromo- or 4-bromopyridinio, carboxypyridinio, for example 3- or 4-carboxypyridinio, sulphopyridinio, for example 3- or 4-sulphopyridinio, cyanopyridinio, for example 3-cyanopyridinio, carboxy-lower alkylcarbamoylpyridinio, for example 3-carboxymethyl-4-carbamoylpyridinio, aminocarbamoylpyridinio, for example 2-amino-5-carbamoylpyridinio, carboxycarbamoylpyridinio, for example 3-carboxy-4-carbamoylpyridinio, cyanohalomethylpyridinio, for example 3-cyano-4-trifluoromethylpyridinio, or aminocarboxypyridinio, for example 2-amino-3-carboxypyridinio.

An ammonio group $R_2$ is preferably pyridinio, or pyridinio substituted by hydroxy-lower alkyl, for example hydroxymethyl, carboxy, carboxy-lower alkyl, for example carboxymethyl, halogen, for example chlorine or bromine, or by carbamoyl, for example 3- or 4-hydroxymethylpyridinio, 4-carboxypyridinio, 3- or 4-carboxymethylpyridinio, 3- or 4-chloropyridinio, 3- or 4-bromopyridinio or 3- or 4-carbamoylpyridinio.

In a group of the formula —CH=CH—$R_2$, the etherified mercapto group $R_2$ has the meanings given hereinbefore, for example heterocyclylthio. $R_2$ preferably presents 5,6-dioxotetrahydro-as-triazinylthio substituted by lower alkoxy, for example methoxy, for example 4-methoxy-5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio.

Protected carboxy $R_3$ may be carboxy esterified by one of the carboxy-protecting groups described in the following, especially esterified carboxy that can be cleaved under physiological conditions.

An esterified carboxy group $R_3$ that can be cleaved under physiological conditions is especially an acyloxy-lower alkoxycarbonyl group in which acyl represents for example, the acyl group of an organic carboxylic acid, especially an optionally substituted lower alkanecarboxylic acid, or in which acyloxymethyl forms the radical of a lactone.

An esterified carboxy group $R_3$ of this type is preferably lower alkanoyloxy-lower alkoxycarbonyl, for example lower alkanoyloxymethoxycarbonyl or lower alkanoyloxyethoxycarbonyl, for example acetoxymethoxycarbonyl, pivaloyloxymethoxycarbonyl or 2-propionyloxyethoxycarbonyl, lower alkoxycarbonyloxy-lower alkoxycarbonyl, for example 1-ethoxycarbonyloxyethoxy-carbonyl or tert.-butoxycarbonyloxymethoxycarbonyl, amino-lower alkanoyloxymethoxycarbonyl, especially $\alpha$-amino-lower alkanoyloxymethoxycarbonyl, for example glycyloxymethoxycarbonyl, L-valyloxymethoxycarbonyl or L-leucyloxymethoxycarbonyl, and also phthalidyloxycarbonyl, for example 2-phthalidyloxycarbonyl, or indanyloxycarbonyl, for example 5-indanyloxycarbonyl.

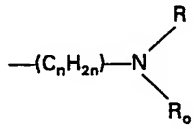
An organic radical $R_5$ that is bonded by a carbon atom to the sulphonyl group may have up to 18 carbon atoms and is an unsubstituted or substituted, saturated or unsaturated, aliphatic, cycloaliphatic or cycloaliphatic-aliphatic hydrocarbon radical, an unsubstituted or substituted aromatic or aromatic-aliphatic hydrocarbon radical or is an unsubstituted or substituted heterocyclyl or heterocyclyl-aliphatic radical.

A saturated aliphatic hydrocarbon radical $R_5$ is, for example, lower alkyl having from 1 to 7, preferably from 1 to 4, carbon atoms, for example methyl, ethyl, n-propyl, isopropyl or n-butyl or is lower alkyl substituted by one, two or more functional or modified functional groups, for example by hydroxy, etherified hydroxy, for example lower alkoxy, for example methoxy, ethoxy or tert.-butoxy, or lower alkenyloxy, for example vinyloxy or allyloxy, esterified hydroxy, for example lower alkanoyloxy, for example acetoxy, or halogen, for example chlorine, etherified mercapto, for example lower alkylthio, for example methylthio or ethylthio, or lower alkylthio in which lower alkyl is substituted by amino and carboxy, for example 2-amino-2-carboxyethylthio, or heterocyclylthio, heterocyclyl being defined in the same manner as a heterocyclyl radical in a heterocyclyl group $R_2$ above, lower alkanoyl, for example acetyl, aroyl, for example benzoyl, carboxy, esterified carboxy, for example lower alkoxycarbonyl, amidated carboxy, for example carbamoyl, lower alkylcarbamoyl, for example methylcarbamoyl, di-lower alkylcarbamoyl, for example dimethylcarbamoyl, cyano, sulpho, lower alkanesulphonyl, for example methanesulphonyl, sulphamoyl, lower alkylsulphamoyl, for example methylsulphamoyl, di-lower alkylsulphamoyl, for example dimethylsulphamoyl, amidino, guanidino, or amino together with one or two of the mentioned functional groups, where possible the substituents being in a position higher than the 1-position of the lower alkyl radical.

Lower alkyl that is substituted by one, two or more functional or modified functional groups is, for example, hydroxy-lower alkyl, for example hydroxymethyl or 2-hydroxyethyl, lower alkoxy-lower alkyl, for example methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl, lower alkenyloxy-lower alkyl, for example 2-vinyloxyethyl, lower alkanoyloxy-lower alkyl, for example 2-acetoxyethyl, halo-lower alkyl, for example chloromethyl, 2-chloroethyl, 3-chloropropyl, 4-chlorobutyl or 2-bromoethyl, lower alkylthio-lower alkyl, for example 2-methylthioethyl or 2-ethylthioethyl, aminocarboxy-lower alkylthio-lower alkyl, for example 2-(2-amino-2-carboxyethylthio)-ethyl, benzoyl-lower alkyl, for example

benzoylmethyl, carboxy-lower alkyl, for example carboxymethyl or 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, for example ethoxycarbonylmethyl or 2-ethoxycarbonylethyl, carbamoyl-lower alkyl, for example carbamoylmethyl, cyano-lower alkyl, for example cyanomethyl or 1-cyano- or 2-cyano-ethyl, sulpho-lower alkyl, for example sulphomethyl or 2-sulphoethyl, sulphamoyl-lower alkyl, for example sulphamoylmethyl or 2-sulphamoylethyl, or is aminocarboxy-lower alkyl, for example 2-amino-2-carboxyethyl.

Lower alkyl that is substituted by a functional or modified functional group preferably has the partial formula



(A)

in which *n* is an integer from 1 to 4, R represents hydrogen, lower alkyl, sulpho, sulpho present in salt form, or an acyl group, and $R_o$ represents hydrogen or lower alkyl, or in which the nitrogen atom is a constituent of a heterocycle and R and $R_o$ together represent alkylene that is optionally interrupted by oxygen, sulphur

or by lower alkyl-substituted, for example methyl-substituted, nitrogen.

The group $-(C_nH_{2n})-$ is an unbranched or branched alkylene chain and is, for example, methylene, 1,2-ethylene, 1,3-propylene, or 1,4-butylene, and also 1,1-ethylene, 1,1-propylene, 1,2-propylene, 1,1-butylene or 1,1-isobutylene.

Lower alkyl R has from 1 to 7 carbon atoms and is, for example, methyl, ethyl, isopropyl, n-propyl, isobutyl, tert.-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl.

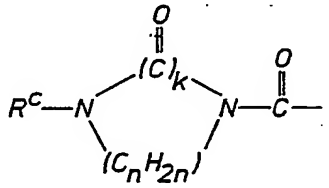
Sulpho R present in salt form is, for example, sulpho in the form of an alkali metal salt, for example a sodium salt, or in the form of an ammonium salt.

An acyl group R may have up to 19 carbon atoms and is especially the acyl group R of a carboxylic acid, a semi-ester of carbonic acid, carbamic acid, a substituted carbamic acid, thiocarbamic acid, a substituted thiocarbamic acid, a sulphonic acid, amidosulphonic acid or of a substituted amidosulphonic acid, or is an acylcarbamoyl or acylthiocarbamoyl group.

An acyl group R of this type has, for example, the partial formula:

$R^a—CO—$, $R^a—O—CO—$, $(R^a)R^bN—CO—$, $(R^a)R^bN—CS—$, $R^a—SO_2—$,

$(R^a)R^bN—SO_2—$, $(R^a—CO)—R^bN—CO—$, $(R^a—CO)—R^bN—CS—$ or



(B)

in which *n* is an integer from 1 to 4, preferably 2, *k* is 1 or 2, each of $R^a$ and $R^b$, independently of the other represents hydrogen, an unsubstituted or substituted, saturated or unsaturated, aliphatic, cycloaliphatic or cycloaliphatic-aliphatic hydrocarbon radical having up to 18, preferably up to 10, carbon atoms, an unsubstituted or substituted, aromatic or aromatic-aliphatic hydrocarbon radical having up to 18, preferably up to 10, carbon atoms or an unsubstituted or substituted heterocyclyl or heterocyclyl-lower alkyl radical, and $R^c$ represents hydrogen, lower alkyl, lower alkyl substituted by hydroxy, halogen, carboxy, lower alkoxy or by amino, lower alkenyl, lower alkanoyl, lower alkanesulphonyl or sulphamoyl.

A saturated or unsaturated, aliphatic, cycloaliphatic or cycloaliphatic-aliphatic hydrocarbon radical $R^a$ or $R^b$ is, for example, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl or cycloalkenyl-lower alkyl.

Substituents of such a radical $R^a$ or $R^b$ are, for example, hydroxy, etherified or esterified hydroxy, for example lower alkoxy, for example methoxy or ethoxy, lower alkanoyloxy, for example acetoxy, hydroxysulphonyloxy present in salt form, or halogen, for example chlorine, etherified mercapto, for example lower alkylthio, for example methylthio, carboxy, esterified carboxy, for example lower

alkoxycarbonyl, for example methoxycarbonyl or ethoxycarbonyl, amidated carboxy, for example carbamoyl, cyano, nitro, sulpho present in salt form, amino, lower alkanoylamino, for example acetylamino, lower alkylamino, for example methyl- or ethyl-amino, or di-lower alkylamino, for example dimethylamino.

Lower alkyl $R^a$ or $R^b$ contains up to 7 carbon atoms and is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.-butyl, n-pentyl, n-hexyl or n-heptyl.

Substituted lower alkyl $R^a$ or $R^b$ is especially substituted methyl or is ethyl or propyl, where possible the substituents preferably being in a position higher than the 1-position of the lower alkyl radical.

Substituted lower alkyl $R^a$ or $R^b$ is, for example, hydroxy-lower alkyl, for example hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl, lower alkoxy-lower alkyl, for example lower alkoxymethyl, lower alkoxyethyl or lower alkoxypropyl, for example methoxymethyl, 2-methoxyethyl or 3-methoxypropyl, lower alkanoyloxy-lower alkyl, for example lower alkanoyloxymethyl, lower alkanoyloxyethyl or lower alkanoyloxypropyl, for example acetoxymethyl, propionyloxymethyl, 2-acetoxyethyl or 3-acetoxypropyl, halo-lower alkyl, for example halomethyl, haloethyl or halopropyl, for example 2-chloro- or 2-bromo-ethyl or 3-chloro- or 3-bromo-propyl, hydroxysulphonyloxy-lower alkyl present in salt form, for example in the form of an alkali metal salt, for example a sodium salt, or in the form of an ammonium salt, for example hydroxysulphonyloxymethyl, 2-hydroxysulphonyloxyethyl or 3-hydroxysulphonyloxypropyl, lower alkylthio-lower alkyl, for example methylthiomethyl, 2-methylthioethyl, 2-methylthiopropyl or tert.-butylthiomethyl, carboxy-lower alkyl, for example carboxymethyl or 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, for example lower alkoxycarbonylmethyl or lower alkoxycarbonylethyl, for example methoxycarbonylmethyl, 2-methoxycarbonylethyl, ethoxycarbonylmethyl or 2-ethoxycarbonylethyl, carbamoyl-lower alkyl, for example carbamoylmethyl or 2-carbamoylethyl, lower alkylcarbamoyl-lower alkyl, for example methylcarbamoylmethyl, di-lower alkylcarbamoyl-lower alkyl, for example dimethylcarbamoylmethyl, cyano-lower alkyl, for example cyanomethyl or 2-cyanoethyl, sulpho-lower alkyl present in salt form, for example in the form of an alkali metal salt, for example a sodium salt, or in the form of an ammonium salt, for example sulphomethyl, 2-sulphoethyl or 3-sulphopropyl, amino-lower alkyl, for example aminomethyl or 2-aminoethyl, lower alkanoylamino-lower alkyl, for example acetylaminomethyl or 2-acetylaminoethyl, lower alkylamino-lower alkyl, for example methylaminomethyl or 2-methylaminoethyl, or di-lower alkylamino-lower alkyl, for example dimethylaminomethyl or 2-dimethylaminoethyl.

Lower alkenyl $R^a$ or $R^b$ contains from 2 to 7, especially from 2 to 4, carbon atoms, and is, for example, vinyl, allyl or 2- or 3-butenyl. Substituents in substituted lower alkenyl $R^a$ or $R^b$ may be the same as in substituted lower alkyl.

Lower alkynyl $R^a$ or $R^b$ may contain from 2 to 7, especially from 2 to 4, carbon atoms and is, for example, ethynyl, 1-propynyl or 2-propynyl.

Cycloalkyl $R^a$ or $R^b$ may contain from 3 to 7 carbon atoms and is, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Cycloalkenyl $R^a$ or $R^b$ may contain from 3 to 7 carbon atoms and is, for example, cyclohexenyl, for example 1-cyclohexenyl, or cyclohexadienyl, for example 1,4-cyclohexadienyl.

Cycloalkyl-lower alkyl $R^a$ or $R^b$ may contain from 4 to 9 carbon atoms and is, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl.

Cycloalkyl-lower alkenyl $R^a$ or $R^b$ may contain from 4 to 9 carbon atoms and is, for example, cyclohexylvinyl or cyclohexylallyl.

Cycloalkenyl-lower alkyl $R^a$ or $R^b$ may contain from 4 to 9 carbon atoms and is, for example, 1-cyclohexenylmethyl or 1,4-cyclohexadienylmethyl.

An aromatic or aromatic-aliphatic hydrocarbon radical $R^a$ or $R^b$ is, for example, phenyl, phenyl-lower alkyl, for example benzyl, 2-phenylethyl, diphenylmethyl or trityl, or phenyl-lower alkenyl, for example 3-phenylallyl.

Phenyl, and phenyl-lower alkyl or phenyl-lower alkenyl, can be substituted at the phenyl radical, for example by lower alkyl, for example methyl or ethyl, lower alkoxy, for example methoxy, or halogen, for example fluorine or chlorine, and also by nitro or amino. In a substituted phenyl-lower alkyl or phenyl-lower alkenyl radical $R^a$ or $R^b$, lower alkyl can be substituted in the $\alpha$-position to the phenyl radical, for example by hydroxy, hydroxysulphonyloxy, carboxy, sulpho or amino.

Heterocyclyl $R^a$ or $R^b$ may have up to 10 carbon atoms and up to 4 hetero atoms from the group comprising nitrogen, oxygen and sulphur, and is, for example, aromatic, monocyclic, five- or six-membered aza-, thia-, oxa-, oxaza-, thiaza-, diaza-, thiadiaza-, triaza- or tetraza-cyclyl. Heterocyclyl $R^a$ or $R^b$ is, for example, pyridyl, for example 2- or 4-pyridyl, thienyl, for example 2- or 3-thienyl, furyl, for example 2- or 3-furyl, oxazolyl, for example 2-oxazolyl, thiazolyl, for example 2-thiazolyl, isothiazolyl, for example 2- or 4-isothiazolyl, pyrimidyl, for example 4- or 5-pyrimidyl, thiadiazolyl, for example 1,2,4-thiadiazol-3-yl, 1,2,5-thiadiazol-3-yl or 1,2,4-thiadiazol-3-yl, triazolyl, for example 3-triazolyl, or tetrazolyl, for example 1- or 5-tetrazolyl.

Substituents of the heterocyclyl radical $R^a$ or $R^b$ may be the same as the substituents mentioned hereinbefore for the heterocyclyl group $R_2$.

Heterocyclyl $R^a$ or $R^b$ is preferably pyridyl, for example 3- or 4-pyridyl, thienyl, for example 2- or 3-thienyl, furyl, for example 2- or 3-furyl, aminooxazolyl, for example 2-amino-4-oxazolyl, aminothiazolyl, for example 2-amino-4-thiazolyl, hydroxypyrimidyl, for example 2,6-dihydroxy-1,3-pyrimid-4-yl, aminothiadiazolyl, for example 5-amino-1,2,4-thiadiazolyl-3-yl, hydroxythiadiazolyl, for example 4-hydroxy-1,2,5-thiadiazol-3-yl, and aminotriazolyl, for example 5-amino-1,2,4-triazol-3-yl.

Heterocyclyl-lower alkyl $R^a$ or $R^b$ is, for example, lower alkyl, for example methyl, that is substituted by heterocyclyl $R^a$ or $R^b$ mentioned hereinbefore, for example tetrazolyl-lower alkyl, for example 1H-tetrazol-5-ylmethyl, or aminothiazolyl-lower alkyl, for example 2-amino-1,3-thiazol-4-ylmethyl.

$R^a$ or $R^b$ is especially hydrogen, lower alkyl, for example methyl or ethyl, lower alkyl substituted by hydroxy, lower alkoxy, for example methoxy, halogen, for example fluorine, chlorine or bromine, carboxy, cyano or by amino, for example 1-hydroxyethyl, methoxymethyl, cyanomethyl or aminomethyl, lower alkenyl, for example vinyl, lower alkynyl, for example ethynyl, cycloalkyl, for example cyclopropyl, phenyl, phenyl substituted by amino or nitro, for example 4-aminophenyl, 4-nitrophenyl, 2,4-dinitrophenyl, phenyl-lower alkyl, for example benzyl, phenyl-lower alkyl in which lower alkyl is substituted in the $\alpha$-position to the phenyl radical by hydroxy or amino, for example hydroxy- or amino-benzyl, pyridyl, for example 4-pyridyl, thienyl, for example 2-thienyl, furyl, for example 2-furyl, hydroxypyrimidyl, for example 2,6-dihydroxy-1,3-pyrimid-4-yl, hydroxythiadiazolyl, for example 4-hydroxy-1,2,5-thiadiazol-3-yl, tetrazolyl-lower alkyl, for example tetrazol-5-ylmethyl, or aminothiazolyl-lower alkyl, for example 2-amino-1,3-thiazol-4-ylmethyl.

An acyl group R is preferably the acyl group of a carboxylic acid, for example lower alkanoyl, for example formyl or acetyl, lower alkanoyl substituted by hydroxy, lower alkoxy, for example methoxy, halogen, for example bromine, carboxy, cyano or by amino, for example $\alpha$-hydroxypropionyl, methoxyacetyl, bromoacetyl, carboxyacetyl, cyanoacetyl or glycyl, lower alkenoyl, for example acryloyl, lower alkynoyl, for example propioloyl, cycloalkylcarbonyl, for example cyclopropylcarbonyl, benzoyl, 4-aminobenzoyl, 4-lower alkanoylaminobenzoyl, for example 4-acetylaminobenzoyl, 4-cyanobenzoyl, 4-nitrobenzoyl or 3,4-dinitrobenzoyl, pyridylcarbonyl, for example nicotinoyl or isonicotinoyl, furoyl, for example 2-furoyl, thienylcarbonyl, for example 2-thienylcarbonyl, hydroxypyrimidylcarbonyl, for example 2,6-dihydroxy-1,3-pyrimid-4-ylcarbonyl, hydroxythiadiazolylcarbonyl, for example 4-hydroxy-1,2,5-thiadiazol-3-ylcarbonyl, tetrazolyl-lower alkanoyl, for example 2-tetrazol-5-ylacetyl or aminothiazolyl-lower alkanoyl, for example 2-(2-amino-1,3-thiazol-4-yl)-acetyl, the acyl group of a semi-ester of carbonic acid, for example lower alkoxycarbonyl, for example methoxycarbonyl or isopropoxycarbonyl, lower alkanoyloxy substituted by carboxy and amino, for example 2-amino-2-carboxyethoxycarbonyl, or benzoyloxycarbonyl, the acyl group of a substituted carbamic acid, for example lower alkylcarbamoyl, for example methylcarbamoyl or anilinocarbonyl, the acyl group of a substituted thiocarbamic acid, for example lower alkylthiocarbamoyl, for example methylthiocarbamoyl, the acyl group of a substituted sulphonic acid, for example lower alkanesulphonyl, for example methanesulphonyl, lower alkanesulphonyl substituted by halogen, for example fluorine, for example difluoromethanesulphonyl, benzenesulphonyl, 4-nitrobenzenesulphonyl, 2,4-dinitrobenzenesulphonyl, aminobenzenesulphonyl, for example 4-aminobenzenesulphonyl, an acylcarbamoyl group, for example benzoylcarbamoyl or furoylcarbamoyl, an acylthiocarbamoyl group, for example benzoylthiocarbamoyl or furoylthiocarbamoyl, 2-oxo-1-imidazolidinocarbonyl, 4-lower alkyl-2,3-dioxo-1-piperazinocarbonyl, for example 4-ethyl-2,3-dioxo-1-piperazinocarbonyl, and 4-lower alkylsulphonyl-1-piperazinocarbonyl, for example 4-methylsulphonyl-1-piperazinocarbonyl.

Lower alkyl $R^c$ is, for example, methyl or ethyl.

Lower alkyl $R^c$ substituted by hydroxy, halogen, carboxy, lower alkoxy or amino is, for example, hydroxymethyl, 1- or 2-hydroxyethyl, chloroethyl, trichloroethyl, carboxymethyl, methoxymethyl, aminomethyl or 2-aminoethyl.

Lower alkenyl $R^c$ is, for example, vinyl, allyl or 1-isobutenyl.

Lower alkanoyl $R^c$ is, for example, acetyl.

Lower alkanesulphonyl $R^c$ is, for example, methanesulphonyl or ethanesulphonyl.

$R^c$ is preferably hydrogen, lower alkyl, for example ethyl, or lower alkanesulphonyl, for example methanesulphonyl.

Lower alkyl $R_o$ is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl or tert.-butyl.

In a group of the partial formula A in which the nitrogen atom is a constituent of a heterocycle, R and $R_o$ represent alkylene, for example ethylene, propylene, butylene, pentylene or hexylene, which is optionally interrupted by oxygen, sulphur,


or by lower alkyl-substituted, for example methyl-substituted, nitrogen. A heterocycle of this type can be substituted at the carbon atoms by one or two hydroxy or oxo groups and is, for example, 1-

aziridinyl, 1-pyrrolidinyl, 1-piperidyl, 1H-2,3,4,5,6,7-hexahydroazepinyl, 4-morpholinyl, 4-thiomorpholinyl and preferably 1-piperazinyl or 4-methyl-1-piperazinyl.

A preferred group of the partial formula A is, for example, 2-aminoethyl, 2-lower alkylaminoethyl, for example 2-methylaminoethyl or 2-n-hexylaminoethyl, 2-di-lower alkylaminoethyl, for example 2-dimethylaminoethyl or 2-di-n-hexylaminoethyl 2-sulphoaminoethyl, lower alkanoylaminoethyl, for example 2-formylaminoethyl or 2-acetylaminoethyl, 2-lower alkoxy-lower alkanoylaminoethyl, for example 2-methoxyacetylaminoethyl, 2-halo-lower alkanoylaminoethyl, for example 2-bromoacetylaminoethyl 2-(α-hydroxypropionylamino)-ethyl, 2-glycylaminoethyl, 2-(3-amino-3-carboxypropionylamino)-ethyl, 2-(α-hydroxypropionylamino)-ethyl, 2-glycylaminoethyl, 2-(3-amino-3-carboxypropionylamino)-ethyl, 2-acryloylaminoethyl, 2-propioloylaminoethyl, 2-cyclopropylcarbonylaminoethyl, 2-benzoylaminoethyl, 2-(4-aminobenzoylamino)-ethyl, 2-(4-acetylaminobenzoylamino)-ethyl, 2-(4-cyanobenzoylamino)-ethyl, 2-(4-nitrobenzoylamino)-ethyl, 2-(3,4-dinitrobenzoylamino)-ethyl, 2-mandeloylaminoethyl, 2-phenylglycylaminoethyl, 2-nicotinoylaminoethyl, 2-isonicotinoylaminoethyl, 2-(2-furoylamino)-ethyl, 2-(2-thienylcarbonylamino)-ethyl, 2-(2,6-dihydroxy-1,3-pyrimid-4-ylcarbonylamino)-ethyl, 2-(4-hydroxy-1,2,5-thiadiazol-3-ylcarbonylamino)ethyl, 2-(2-tetrazol-1-ylacetylamino)-ethyl, 2-[2-(2-amino-1,4-thiazol-4-yl)-acetylamino]-ethyl, 2-lower alkoxycarbonylaminoethyl, for example 2-methoxycarbonylaminoethyl or 2-isopropoxycarbonylaminoethyl, 2-(2-amino-2-carboxyethoxycarbonylamino)-ethyl, 2-benzoyloxycarbonylaminoethyl, 2-lower alkylcarbamoylaminoethyl, for example 2-methylcarbamoylaminoethyl, 2-anilinocarbonylaminoethyl, 2-lower alkylthiocarbamoylaminoethyl, for example 2-methylthiocarbamoylaminoethyl, 2-lower alkanesulphonylaminoethyl, for example 2-methanesulphonylaminoethyl, 2-halomethanesulphonylaminoethyl, for example 2-difluoromethanesulphonylaminoethyl, 2-cyanomethanesulphonylaminoethyl, 2-benzenesulphonylaminoethyl, 2-(4-nitrobenzenesulphonylamino)-ethyl, 2-(3,4-dinitrobenzenesulphonylamino)-ethyl, 2-benzoylcarbamoylaminoethyl, 2-(2-furoylcarbamoylamino)-ethyl, 2-(2-oxo-1-imidazolidinocarbonylamino)-ethyl, 2-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-ethyl and 2-(4-methylsulphonylpiperazinocarbonylamino)-ethyl.

An unsaturated aliphatic hydrocarbon radical $R_5$ is, for example, lower alkenyl having from 2 to 5 carbon atoms, for example vinyl or allyl.

A saturated cycloaliphatic hydrocarbon radical $R_5$ is, for example, cycloalkyl having from 3 to 8, especially from 3 to 6, carbon atoms, from example, cyclopropyl, cyclopentyl or cyclohexyl.

An unsaturated cycloaliphatic hydrocarbon radical $R_5$ is, for example, cycloalkenyl having 5 or 6 carbon atoms, for example 1-cyclohexenyl or 1,4-cyclohexadienyl.

An aromatic hydrocarbon radical $R_5$ is, for example, phenyl or naphthyl which can be substituted by the following substituents: alkyl, for example dodecyl or lower alkyl, for example methyl or ethyl, halo-lower alkyl, for example trifluoromethyl, hydroxy, etherified hydroxy, for example lower alkoxy, for example methoxy or ethoxy, esterified hydroxy, for example lower alkanoxyloxy, for example acetoxy, or halogen, for example chlorine, or lower alkoxycarbonyloxy, for example ethoxycarbonyloxy, amino, di-lower alkylamino, for example dimethylamino, lower alkylamino, for example methylamino, lower alkanoylamino, for example formylamino or acetylamino, di-lower alkylaminomethyleneamino, for example dimethylaminomethyleneamino, hydrazino, carbazo, thiocarbamoylhydrazino, lower alkoxycarbonylamino, for example ethoxycarbonylamino, cyano, nitro, carboxy or esterified carboxy, for example methoxycarbonyl or ethoxycarbonyl.

An aromatic hydrocarbon radical $R_5$ is preferably phenyl, naphthyl, 4-alkylphenyl, for example 4-dodecylphenyl, 4-lower alkylphenyl, for example 4-methylphenyl, 3-halo-lower alkylphenyl, for example 3-trifluoromethylphenyl, 4-aminophenyl, 4-lower alkanoylaminophenyl, for example 4-formylaminophenyl or 4-acetylaminophenyl, 4-di-lower alkylaminomethyleneaminophenyl, for example 4-dimethylaminomethyleneaminophenyl, 4-hydrazinophenyl, 4-carbazophenyl, 4-thiocarbamoylhydrazino, 4-lower alkoxycarbonylaminophenyl, for example 4-ethoxycarbonylaminophenyl, 4-nitrophenyl, 4-cyanophenyl, 4-carboxyphenyl, 5-carboxy-6-hydroxy-2-naphthyl, 6-lower alkoxycarbonyloxy-2-naphthyl, for example 6-ethoxycarbonyloxy-2-naphthyl, 5- or 6-alkanoylamino-1-naphthyl, for example 5- or 6-acetylamino-1-naphthyl, 6-lower alkoxycarbonylamino-1-naphthyl, for example 6-ethoxycarbonylamino-1-naphthyl, or 4-lower alkoxycarbonyloxy-6-lower alkoxycarbonylamino-1-naphthyl, for example 4-ethoxycarbonyloxy-6-ethoxycarbonylamino-1-naphthyl.

An aromatic-aliphatic hydrocarbon radical $R_5$ is, for example, one of the mentioned aliphatic radicals, for example lower alkyl, for example methyl or ethyl, that is substituted by one of the mentioned aromatic radicals, for example phenyl, for example benzyl or phenethyl.

Heterocyclyl $R_5$ is, for example, aromatic or hydrogenated, monocyclic or benzo-condensed heterocyclyl, for example monocyclic, aromatic five- or six-membered aza-, thia- or oxa-cyclyl, for example pyridyl, for example 2-, 3- or 4-pyridyl, thienyl, for example 2- or 3-thienyl, or furyl, for example 2- or 3-furyl, monocyclic, aromatic, five- or six-membered diazacyclyl, for example imidazolyl, for example 2-imidazolyl or 5-imidazolyl, pyrimidyl, for example 4- or 5-pyrimidyl, monocyclic, aromatic, five-membered thiadiazacyclyl, for example thiadiazolyl, for example 1,3,4-thiadiazol-5-yl, monocyclic, hydrogenated, five-membered oxacyclyl, for example tetrahydrofuryl, for example 3-tetrahydrofuryl, benzo-condensed azacyclyl, for example indolyl, for example 5-indolyl, benzo-condensed diazacyclyl, for example quinoxalinyl, for example 7-quinoxalinyl, or indazolyl, for example

5-indazolyl, benzo-condensed oxazacyclyl, for example benzoxazolyl, for example 5-benzoxazolyl, or is benzo-condensed thiazacyclyl, for example benzothiazolyl, for example 2-, 5- or 6-benzothiazolyl.

Substituents of a heterocyclyl radical $R_5$ are, for example, oxo, hydroxy, halogen, for example chlorine, lower alkyl, for example methyl, lower alkoxycarbonyl, for example ethoxycarbonyl, lower alkanoylamino, for example acetylamino, or N-lower alkylureido, for example N-methylureido.

Substituted heterocyclyl $R_5$ is, for example, lower alkanoylaminopyridyl, for example 5-acetylaminopyrid-2-yl, lower alkyl-lower alkanoylamino-lower alkoxycarbonylthienyl, for example 3-methyl-4-ethoxy-carbonyl-5-acetylaminothien-2-yl, lower alkylimidazolyl, for example 1-methylimidazol-5-yl, dihydroxypyrimidyl, for example 2,4-dihydroxypyrimid-5-yl, lower alkanoylaminothiadiazolyl, for example 2-acetylamino-1,3,4-thiadiazol-5-yl, lower alkylureidothiadiazolyl, for example 2-methylaminocarbonylamino-1,3,4-thiadiazol-5-yl, lower alkylindolyl, for example 2-methylindol-5-yl, dihydroxyquinoxalinyl, for example 2,3-dihydroxyquinoxalin-7-yl, hydroxyindazolyl, for example 3-hydroxyindazol-5-yl, hydroxychlorobenzoxazolyl, for example 2-hydroxy-6-chlorobenzoxazol-5-yl, or aminobenzothiazolyl, for example 2-aminobenzothiazol-6-yl.

Heterocyclyl $R_6$ is, for example, aromatic, monocyclic, five- or six-membered aza-, thia-, oxa-, thiaza-, diaza-, thiadiaza-, triaza- or tetraza-cyclyl, for example pyridyl, for example 3- or 4-pyridyl, thienyl, for example 2- or 3-thienyl, furyl, for example 2- or 3-furyl, thiazolyl, for example 2-thiazolyl, isothiazolyl, for example 2- or 4-isothiazolyl, pyrimidyl, for example 4- or 5-pyrimidyl, thiadiazolyl, for example 1,2,4-thiadiazol-3-yl, 1,2,5-thiadiazol-3-yl, or 1,3,4-thiadiazol-3-yl, triazolyl, for example 3-triazolyl, or tetrazolyl, for example 1- or 5-tetrazolyl.

Substituents of the heterocyclyl radical $R_6$ may be the same substituents as those mentioned herebefore for the heterocyclylthio group $R_2$.

Heterocyclyl $R_6$ is preferably pyridyl, for example 3- or 4-pyridyl, thienyl, for example 2- or 3-thienyl, furyl, for example 2- or 3-furyl, aminothiazolyl, for example 2-amino-4-thiazolyl, hydroxypyrimidyl, for example 2,6-dihydroxy-1,3-pyrimid-4-yl, aminothiadiazolyl, for example 5-amino-1,2,4-thiadiazol-3-yl, hydroxythiadiazolyl, for example 4-hydroxy-1,2.5-thiadiazol-3-yl, or aminotriazolyl, for example 5-amino-1,2,4-triazol-3-yl.

A heterocyclyl-aliphatic radical $R_6$ is, for example, lower alkyl, for example methyl, that is substituted by heterocyclyl $R_6$ mentioned hereinbefore, for example tetrazolyl-lower alkyl, for example tetrazol-5-ylmethyl, or aminothiazolyl-lower alkyl, for example 2-amino-1,3-thiazol-4-ylmethyl.

The functional groups present in compounds of the formula I, especially the carboxy, amino, hydroxy and sulpho groups, are optionally protected by those protecting groups (conventional protecting groups) which are customarily used in penicillin, cephalosporin and peptide chemistry.

The protection of functional groups by such protecting groups, the protecting groups themselves, and reactions for their removal, are described, for example, in "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in "Protective Groups in Organic Chemistry", Wiley, New York 1974, in "The Peptides", Vol. I, Schröder and Lubke, Academic Press, London and New York 1965, and in "Methoden der organischen Chemie", Houben-Weyl, 4th Edition, Vol. 15/I, Georg Thieme Verlag, Stuttgart 1974.

Such protecting groups can readily be removed under mild conditions, that is to say with little or no occurrence of undesirable secondary reactions for example by means of solvolysis, reduction or photolysis or alternatively under physiological conditions.

A carboxy group, for example the carboxy group $R_3$, and also a carboxy group present in $R_2$, $R_5$ or $R_6$, is customarily protected in esterified form, the ester group being readily removable under mild conditions. A carboxy group protected in esterified form is esterified especially by a lower alkyl group that is branched in the 1-position or is substituted in the 1- or 2-position by suitable substituents.

A protected carboxy group esterified by a lower alkyl group that is branched in the 1-position is, for example, tert.-lower alkoxycarbonyl, for example tert.-butoxycarbonyl, arylmethoxycarbonyl having one or two aryl radicals wherein aryl preferably represents phenyl that is unsubstituted or mono-, di- or tri-substituted, for example by lower alkyl, for example tert.-lower alkyl, for example, tert.-butyl, lower alkoxy, for example methoxy, hydroxy, halogen, for example chlorine, and or by nitro, for example benzyloxycarbonyl, benzyloxycarbonyl substituted by the mentioned substituents, for example 4-nitrobenzyloxycarbonyl or 4-methoxybenzyloxycarbonyl, diphenylmethoxycarbonyl or diphenylmethoxycarbonyl substituted by the mentioned substituents, for example di-(4-methoxyphenyl)-methoxycarbonyl.

A protected carboxy group esterified by a lower alkyl group that is substituted in the 1- or 2-position by suitable substituents is, for example, 1-lower alkoxy-lower alkoxycarbonyl, for example methoxymethoxycarbonyl, 1-methoxyethoxycarbonyl or 1-ethoxymethoxycarbonyl, 1-lower alkylthio-lower alkoxycarbonyl, for example 1-methylthiomethoxycarbonyl or 1-ethylthioethoxycarbonyl, aroylmethoxycarbonyl, for example phenacyloxycarbonyl, and 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl.

A carboxy group can also be protected in the form of an organic silyloxycarbonyl group. An organic silyloxycarbonyl group is, for example, a tri-lower alkylsilyloxycarbonyl group, for example trimethylsilyloxycarbonyl. The silicon atom of the silyloxycarbonyl group can instead be substituted by two lower alkyl groups, for example methyl groups, and the carboxy group or amino group of a second

molecule of the formula I. Compounds having such protecting groups can be manufactured, for example, using dimethyldichlorosilane as silylating agent.

A protected carboxy group is preferably tert.-lower alkoxycarbonyl, for example tert.-butoxycarbonyl, benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl or diphenylmethoxycarbonyl.

An amino group, for example an amino group present in $R_2$, $R_5$ or $R_6$, can be protected, for example, in the form of a readily cleavable acylamino, arylmethylamino, etherified mercaptoamino, 1-acyl-lower alk-1-en-2-ylamino or silylamino group.

In a readily cleavable acylamino group, acyl is, for example, the acyl group of an organic carboxylic acid having up to 10 carbon atoms, especially of a lower alkanecarboxylic acid that is unsubstituted or substituted, for example, by halogen or aryl, or of a benzoic acid that is unsubstituted or substituted, for example, by halogen, lower alkoxy or nitro, or of a carbonic acid semi-ester. Such an acyl group is, for example, lower alkanoyl, for example formyl, acetyl or propionyl, halo-lower alkanoyl, for example 2-haloacetyl, especially 2-chloro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro-, or 2,2,2-trichloroacetyl, benzoyl, or benzoyl substituted, for example, by halogen, for example chlorine, lower alkoxy or nitro, for example benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl or 4-nitrobenzoyl, or lower alkoxycarbonyl that is branched in the 1-position of the lower alkyl radical or substituted in the 1- or 2-position by suitable substituents.

Lower alkoxycarbonyl branched in the 1-position of the lower alkyl radical is, for example, tert.-lower alkoxycarbonyl, for example tert.-butoxycarbonyl, arylmethoxycarbonyl having one or two aryl radicals wherein aryl is preferably phenyl that is unsubstituted or mon-, di- or tri-substituted, for example, by lower alkyl, especially tert.-lower alkyl, for example tert.-butyl, lower alkoxy, for example methoxy, hydroxy, halogen, for example chlorine, and/or by nitro, for example diphenylmethoxycarbonyl or di-(4-methoxyphenyl)-methoxycarbonyl.

Lower alkoxycarbonyl substituted in the 1- or 2-position by suitable substituents is, for example, aroylmethoxycarbonyl, for example phenacyloxycarbonyl, 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodoethoxycarbonyl or 2-(tri-substituted silyl)-ethoxycarbonyl in which the silyl group is substituted by organic radicals, for example lower alkyl, phenyl-lower alkyl or phenyl, for example 2-tri-lower alkylsilylethoxycarbonyl, for example 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methyl-silyl)-ethoxycarbonyl, or 2-triphenylsilylethoxycarbonyl.

Arylmethylamino is, for example, mono-, di- or, especially, tri-phenylmethylamino. Arylmethylamino is, for example, benzyl-, diphenylmethyl- and, especially, trityl-amino.

In an etherified mercaptoamino group, the etherified mercapto group is especially arylthio, for example 4-nitrophenylthio.

In a 1-acyl-lower alk-1-ene-2-amino group, acyl is, for example, the acyl group of a lower alkanecarboxylic acid or of a carbonic acid lower alkyl semi-ester. Such amino-protecting groups are especially 1-lower alkanoylprop-1-en-2-yl, for example 1-acetylprop-1-en-2-yl, or 1-lower alkoxycarbonylprop-1-en-2-yl, for example 1-ethoxycarbonylprop-1-en-2-yl.

A silylamino group is, for example, a tri-lower alkylsilylamino group, for example trimethylsilylamino. The silicon atom of the silylamino group can instead be substituted by only two lower alkyl groups, for example methyl groups, and by the amino groups or carboxy group of a second molecule of the formula I. Compounds having such protecting groups can be manufactured, for example, using dimethyldichlorosilane as silylating agent.

An amino group can also be protected in protonated form. Especially suitable anions for this purpose are those of strong inorganic acids, such as hydrohalic acids, for example the chlorine or bromine anion, or of organic sulphonic acids such as *p*-toluenesulphonic acid.

A protected amino group is preferably tert.-butoxycarbonylamino (BOC), 4-nitrobenzyloxycarbonylamino, diphenylmethoxycarbonylamino, 2-halo-lower alkoxycarbonylamino, for example 2,2,2-trichloroethoxycarbonylamino, tritylamino and formylamino.

A hydroxy group, for example a hydroxy group present in $R_2$, $R_5$ or $R_6$, can be protected, for example, by an acyl group, for example by halo-substituted lower alkanoyl, for example 2,2-dichloroacetyl, or especially by an acyl radical of a carbonic acid semi-ester mentioned for protected amino groups. A preferred hydroxy-protecting group is, for example, 2,2,2-trichloroethoxycarbonyl, 4-nitrobenzyloxycarbonyl, an organic silyl radical having the substituents mentioned hereinbefore, for example trimethylsilyl or dimethyl-n-butyl-silyl, and also a readily removable, etherifying group, such as tert.-lower alkyl, for example tert.-butyl, a 2-oxa- or a 2-thia-aliphatic or -cycloaliphatic hydrocarbon radical, for example 1-lower alkoxy-lower alkyl or 1-lower alkylthio-lower alkyl, for example methoxymethyl, 1-methoxyethyl 1-ethoxyethyl, 1-methylthiomethyl, 1-methylthioethyl or 1-ethylthioethyl, or 2-oxa- or 2-thia-cycloalkyl having from 5 to 7 ring atoms, for example 2-tetrahydrofuryl or 2-tetrahydropyranyl, or a corresponding thia analogue, and 1-phenyl-lower alkyl, for example benzyl or diphenylmethyl, it being possible for the phenyl radicals to be substituted, for example, by halogen, for example chlorine, lower alkoxy, for example methoxy, and/or by nitro.

A sulphur group, for example a sulpho group present in $R_2$, $R_5$ or $R_6$, is preferably protected by a tert.-lower alkyl group, for example tert.-butyl, or by a silyl group, for example by tri-lower alkylsilyl. A sulpho group can be protected, for example, by carboxy-protecting groups.

Salts are especially pharmaceutically acceptable or useful, non-toxic salts of compounds of the formula I.

Such salts are formed, for example, from the acidic groups present in compounds of the formula I, for example carboxy or sulpho groups, and are especially metal or ammonium salts, for example alkali metal and alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, and ammonium salts, which are formed with ammonia or suitable organic amines, there being suitable for the salt formation especially aliphatic, cycloaliphatic, cycloaliphatic-aliphatic or araliphatic, primary, secondary or tertiary mono-, di- or poly-amines, and also heterocyclic bases. Such bases are, for example, lower alkylamines, for example triethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tris-(2-hydroxyethyl)-amine, basic aliphatic esters of carboxylic acids, for example 4-aminobenzoic acid 2-diethyldiaminoethyl ester, lower alkeneamines, for example 1-ethylpiperidine, cycloalkylamines, for example dicyclohexylamine, or benzylamines, for example N,N'-dibenzylethylenediamine, and also bases of the pyridine type, for example pyridine, collidine or quinoline.

The basic groups present in compounds of the formula I, for example amino groups, can form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulphuric acid or phosphoric acid, or with suitable organic carboxylic or sulphonic acids, for example trifluoroacetic acid, and with amino acids, such as arginine and lysine.

If the compounds of the formula I contain several acidic groups, for example two carboxy groups, or several basic groups, for example two amino groups, mono- or poly-salts can be formed. If the compounds of the formula I contain at least one acidic group, for example the carboxy group $R_3$, and at least one basic group, for example an amino group in $R_5$ or $R_6$, then the compounds may be in the form of internal salts, that is to say in zwitterion form. In compounds of the formula I, one acidic and one basic group may form an internal salt, and additional acidic and/or basic groups can be, for example, in the form of acid addition salts and/or base addition salts.

For the purpose of isolation or purification, it is possible to use also pharmaceutically unacceptable salts. Only pharmaceutically acceptable, non-toxic salts are used therapeutically, however, and these are therefore preferred.

The compounds of the formula I in which the functional groups are in free form and the carboxy groups are optionally in physiologically cleavable esterified form, and their pharmaceutically acceptable non-toxic salts are valuable antibiotically active ingredients that can be used especially as antibacterial antibiotics.

For example, they are effective *in vitro* against gram-positive and gram-negative micro-organisms, including strains producing β-lactamase, for example against cocci, such as *Staphylococcus aureus, Streptococcus pneuomoniae, Streptococcus pyogenes* and *Neisseria gonorrhoeae,* in minimum concentrations of from approximately 0.001 to approximately 32 μg/ml, against enterobaceteria, for example *Escherichia coli, Salmonella typhimurium, Klebsiella pneumoniae, Proteus spp., Enterobacter cloacae, Serratia marcescens, Haemophilus influenzae* and *Pseudomonas aeruginosa*, and against anaerobic gram-positive and gram-negative bacterial, for example *Bacteroides fragilis* or *Clostridium perfringens*, in minimum concentrations of from approximately 0.001 to approximately 64 μg/ml. *In vivo*, when administered subcutaneously to mice, they are effective, for example, against systemic infections caused by cocci, for example *Staphylococcus aureus*, in a dosage range of from approximately 3 mg/kg to approximately 100 mg/kg, and against systemic infections caused by enterobacteria, for example *Escherichia coli, Proteus morganii* or *Pseudomonas aeruginosa*, in a dosage range of from approximately 0.1 mg/kg to approximately 100 mg/kg.

In the following experimental report, the effectiveness of compounds of the formula I is demonstrated with reference to selected compounds:

**Experimental report**

**I. Tested compounds**

The antibiotic activity of the following compounds was tested:

1. The sodium salt of 3-methoxy-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 16a).

2. The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)acetamido]-3-cephem-4-carboxylic acid (Example 13a).

3. The sodium salt of 7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 14a).

4. The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 15a).

5. The sodium salt of 3-(1-carboxymethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid Example 18).

6. The sodium salt of 3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-

aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 19).

7. The sodium salt of 7β-[(2R,S)-2-(2-methanesulphonylaminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 21a).

8. The sodium salt of 2-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (Example 22a).

9. 3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (Example 23a).

10. The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 25a).

11. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 27a).

12. The sodium salt of 3-(1-methyl-1H-tetrasol-5-ylthiomethyl)-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 28a).

13. The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 28b).

14. The sodium salt of 7β-[(2R,S)-2-(2-(2-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 29a).

15. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 31a).

16. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 34a).

17. The sodium salt of 7β-[(2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 38a).

18. 7β-[(2R,S)-2-(2-methylaminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 42a).

19. 7β-[(2R,S)-2-(2-methoxyethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 43a).

20. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid (Example 44a).

21. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxymalonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 50a).

22. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-bromoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 51a).

23. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzoylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 55a).

24. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-acetamidobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 56a).

25. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 58a).

26. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 24a).

27. 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-butyrylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 30a).

28. The sodium salt of 7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 32a).

29. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 35a).

30. The sodium salt of 7β-[(2S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid (Example 8a).

31. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 33a).

32. The sodium salts of 3-acetoxymethyl-7β-[(2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 39a).

33. The sodium salt of 7β-[(2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid (Example 40a).

34. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(5-imidazolesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 65a).

35. The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 67a).

36. The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 68a).

37. The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (Example 71a).

38. 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester (Example 72a).

39. The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 73a).

40. The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (Example 75a).

41. The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 85a).

42. The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 87b).

43. The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 90a).

44. The disodium salt of 3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (Example 95).

45. The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 103a).

46. The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 105a).

47. The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (Example 106).

**II. Experimental procedure**

A. The antibiotic activity of the test compounds *in vitro* was established by the agar dilution method according to Ericsson, H. M., and Sherris, S. C., *1971*, Acta Path, Microb. Scand. Section B. Suppl. No. 217, vol. 1—90, in DST agar. The minimum concentrations still inhibiting the growth of the test organisms (MIC=minimum inhibitory concentration) are given in micrograms per millilitre (μg/ml) for the tested compounds in Table 1.

B. The chemotherapeutic activity *in vivo* against systemic infections in female SPF, $MF_2$ mice was established according to the method of Zak, O., *et al., 1979*, Drugs Exptl. Clin. Res. *5*, 45—59. The $ED_{50}$ values found in milligrams substance per kilogram mouse (mg/kg) for a number of micro-organisms are indicated in Table 2 for the test compounds administered orally (p.o.) or subcutaneously (s.c.).

**III Test results**

**Table 1**
**Antibiotic activity (in vitro)**

| | MIC [µg/ml] | | | |
|---|---|---|---|---|
| *Test compound* | *Escherichia coli 205* | *Klebsiella pneumoniae 327* | *Salmonella typhimurium 277* | *Neisseria gonorrhoeae 1317/4* |
| 1 | 0.5 | 0.5 | 0.5 | 0.1 |
| 2 | 0.02 | 0.02 | 0.02 | 0.005 |
| 3 | 0.02 | 0.1 | 0.02 | 0.02 |
| 4 | 0.02 | 0.1 | 0.02 | 0.005 |
| 5 | 0.1 | 0.1 | 0.1 | 0.001 |
| 6 | 0.1 | 0.1 | 0.05 | 0.005 |
| 7 | 0.02 | 0.02 | 0.02 | 0.02 |
| 8 | 0.01 | 0.01 | 0.01 | 0.001 |
| 9 | 0.1 | 0.2 | 0.1 | 0.001 |
| 10 | 0.05 | 0.05 | 0.05 | n.t. |
| 11 | 0.01 | 0.01 | 0.01 | 0.005 |
| 12 | 0.05 | 0.05 | 0.05 | 0.002 |
| 13 | 0.005 | 0.01 | 0.01 | 0.001 |
| 14 | 0.02 | 0.05 | 0.02 | 0.001 |
| 15 | 0.01 | 0.05 | 0.01 | 0.01 |
| 16 | 0.05 | 0.05 | 0.02 | 0.01 |
| 17 | 0.5 | 0.5 | 0.2 | 0.002 |
| 18 | 0.01 | 0.01 | 0.01 | 0.01 |
| 19 | 0.05 | 0.05 | 0.02 | n.t. |
| 20 | 0.02 | 0.05 | 0.01 | 0.01 |
| 21 | 0.05 | 0.05 | 0.02 | 0.01 |
| 22 | 0.05 | 0.05 | 0.05 | 0.02 |
| 23 | 1.0 | 1.0 | 1.0 | 0.05 |
| 24 | 0.05 | 0.2 | 0.1 | n.t. |
| 25 | 0.05 | 0.1 | 0.05 | 0.001 |
| 26 | 0.01 | 0.02 | 0.01 | n.t. |
| 27 | 0.05 | 0.05 | 0.05 | n.t. |
| 28 | 0.05 | 0.05 | 0.02 | n.t. |
| 29 | 0.05 | 0.05 | 0.05 | 0.01 |
| 30 | 0.02 | 0.02 | 0.01 | 0.005 |
| 31 | 0.01 | 0.01 | 0.01 | n.t. |
| 32 | 1 | 1 | 1 | 0.01 |
| 33 | 0.02 | 0.05 | 0.02 | 0.02 |
| 34 | 0.05 | 0.2 | 0.05 | n.t. |
| 35 | 0.5 | 1 | 0.5 | 0.01 |
| 36 | 0.05 | 0.1 | 0.05 | 0.01 |
| 37 | 0.02 | 0.05 | 0.05 | 0.002 |
| 38 | 0.01 | 0.02 | 0.01 | 0.002 |
| 39 | 0.01 | 0.02 | 0.01 | 0.002 |
| 40 | 0.005 | 0.01 | 0.005 | 0.001 |
| 41 | 0.05 | 0.05 | 0.05 | 0.002 |
| 42 | 0.01 | 0.01 | 0.01 | 0.002 |
| 43 | 0.01 | 0.05 | 0.05 | 0.002 |
| 44 | 0.1 | 0.05 | 0.1 | 0.001 |
| 45 | 0. 02 | 0.02 | 0.01 | 0.002 |
| 46 | 0.01 | 0.05 | 0.02 | 0.002 |
| 47 | 0.05 | 0.1 | 0.05 | 0.005 |

**Table 2**
**Chemotherapeutic activity (*in vivo*)**

| *Test compound* | $ED_{50}$ *[mg/kg, s.c./p.o.] or [mg/kg, s.c.]* | |
|---|---|---|
| | *Staphylococcus aureus 10 B* | *Escherichia coli 205* |
| 1 | >30 | 25/80 |
| 2 | 18 | 0.3/4.0 |
| 3 | 18 | 0.9/2.2 |
| 4 | 20 | 0.35/5.5 |
| 5 | >30 | 0.2/3.0 |
| 6 | >30 | <1 |
| 7 | 30 | 0.9/3 |
| 8 | 13 | 1.5/6 |
| 9 | 7 | <1/10 |
| 10 | n.t. | <1.0/6 |
| 11 | >30 | 0.35/1.6 |
| 12 | 15 | 0.87/7 |
| 13 | 14 | 0.35/3.5 |
| 14 | 30 | 1.8/10 |
| 15 | 85 | 2.0/7 |
| 16 | 10 | 1/4.8 |
| 17 | 43 | 18/>30 |
| 18 | 78 | 0.45/2 |
| 19 | >30 | 6.0/10 |
| 20 | >30 | 0.8/8 |
| 21 | >100 | 2.0/9 |
| 23 | 55 | 25 |
| 24 | 90 | 2.5 |
| 25 | >100 | 1.0 |
| 26 | >30 | 0.5/3 |
| 27 | >30 | 7/25 |
| 28 | 60 | 2.2 |
| 29 | 44 | <1 |
| 30 | 30 | 0.6/2.3 |
| 31 | 22 | 1.5/8 |
| 32 | 10 | 3 |
| 33 | 20 | <1 |
| 34 | >30 | 10 |
| 35 | 10 | 2 |
| 36 | 30 | n.t. |
| 37 | 15 | 2/13 |
| 38 | 15 | 0.9/2.8 |
| 39 | 10 | 0.8/5.5 |
| 40 | 3 | 0.1/0.9 |
| 41 | 24 | 2/10 |
| 42 | 15 | 0.1/2.5 |
| 43 | 50 | 1/8 |
| 44 | 85 | <1 |
| 45 | 55/90 | n.t. |
| 46 | 9 | <1/14 |
| 47 | 5/100 | 2.8/>30 |

(n.t.=not tested)

Compounds of the formula I in which the functional groups are protected are used as starting materials for the manufacture of compounds of the formula I in which functional groups are present in free form or in physiologically cleavable form.

The present invention preferably relates to those compounds of the formula I in which functional groups are present in free form or in physiologically cleavable protected form, and to their pharmaceutically acceptable salts, since it is mainly these compounds which have the indicated activity and can be used for the purpose specified.

The invention relates especially to compounds of the formula I in which *m* is an integer from 0 to 2, $R_1$ represents hydrogen, lower alkyl, for example methyl, lower alkoxy, for example methoxy or ethoxy, halogen, for example chlorine, or a group of the formula —$CH_2$—$R_2$ wherein $R_2$ represents lower alkanoyloxy, for example acetoxy, carbamoyloxy, lower alkylcarbamoyloxy, or aromatic, monocyclic, five- or six-membered heterocyclylthio, for example diaza-, triaza-, tetraaza-, thiaza-, thiadiaza-, oxaza- or oxadiaza-cyclylthio, for example imidazolylthio, triazolylthio, for example 1H-1,2,3-triazol-5-ylthio, tetrazolylthio, for example 1H-tetrazol-5-ylthio, thiazolylthio, thiadiazolylthio, for example 1,3,4-thiadiazol-5-ylthio, oxazolylthio, oxadiazolylthio or 5,6-dioxotetrahydro-as-triazin-3-ylthio, for example 5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio or 5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio, which can be substituted by lower alkyl, for example methyl, di-lower alkylamino-lower alkyl, for example dimethylaminomethyl or 2-dimethylaminoethyl, sulpho-lower alkyl, for example sulphomethyl or sulphoethyl, carboxy-lower alkyl, for example carboxymethyl, amino, carboxy-lower alkylamino, for example 2-carboxyethylamino, carbamoyl, or by tetrazolyl-lower alkyl, for example tetrazol-1H-5-ylmethyl, or $R_2$ represents an ammonio group, for example 2-lower alkyl-1-pyrazolio, for example 2-methyl-1-pyrazolio, 2-carboxy-lower alkyl-1-pyrazolio, for example 2-carboxymethyl-1-pyrazolio, 3-lower alkyl-1-triazolio, for example 3-methyl-1-triazolio, pyridinio, pyridinio substituted by hydroxy-lower alkyl, for example hydroxymethyl, carboxy, carboxy-lower alkyl, for example carboxymethyl, halogen, for example chlorine or bromine, or by carbamoyl, for example 3- or 4-hydroxymethylpyridinio, 4-carboxypyridinio, 3- or 4-carboxymethylpyridinio 3- or 4-chloropyridinio, 3- or 4-bromopyrimidinio or 3- or 4-carbamoyl-pyridinio, $R_3$ represents carboxy or carboxy that can be cleaved under physiological conditions, for example acyloxy-lower alkoxycarbonyl, for example lower alkanoyloxy-lower alkoxycarbonyl, for example lower alkanoyloxymethoxycarbonyl or lower alkanoyloxyethoxycarbonyl, for example pivaloyloxymethoxycarbonyl or 2-propionyloxyethoxycarbonyl or lower alkoxycarbonyloxy-lower alkoxycarbonyl, for example 1-ethoxycarbonyloxyethoxycarbonyl or tert.-butoxy-carbonyloxymethoxycarbonyl, $R_4$ represents hydrogen, $R_5$ represents lower alkyl, for example methyl or ethyl, hydroxy-lower alkyl, for example hydroxymethyl or 2-hydroxyethyl, lower alkoxy-lower alkyl, for example methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl, lower alkenyl-oxy-lower alkyl, for example 2-vinyloxyethyl, lower alkanoyloxy-lower alkyl, for example 2-acetoxyethyl, halo-lower alkyl, for example chloromethyl, 2-chloroethyl, 3-chloropropyl, 4-chlorobutyl or 2-bromoethyl, lower alkylthio-lower alkyl, for example 2-methylthioethyl or 2-ethylthioethyl, amino-carboxy-lower alkylthio-lower alkyl, for example 2-(2-amino-2-carboxyethylthio)-ethyl, benzoyl-lower alkyl, for example benzoylmethyl, carboxy-lower alkyl, for example carboxymethyl or 2-carboxyethyl, lower alkoxycarbonyl-lower alkyl, for example ethoxycarbonylmethyl or 2-ethoxycarbonylethyl, carbamoyl-lower alkyl, for example carbamoylmethyl, cyano-lower alkyl, for example cyanomethyl or 1-cyano- or 2-cyano-ethyl, sulpho-lower alkyl, for example sulphomethyl or 2-sulphoethyl, sulphamoyl-lower alkyl, for example sulphamoylmethyl or 2-sulphamoylethyl, aminocarboxy-lower alkyl, for example 2-amino-2-carboxyethyl, or a group of the partial formula A in which the group —$(C_nH_{2n})$— represents ethylene or propylene, $R_6$ represents hydrogen or lower alkyl, for example methyl, and R represents hydrogen, lower alkyl, for example methyl or ethyl, lower alkanoyl, for example formyl or acetyl, lower alkanoyl substituted by hydroxy, lower alkoxy, for example methoxy, halogen, for example bromine, carboxy, cyano or by amino, for example α-hydroxypropionyl, methoxyacetyl, bromoacetyl, carboxyacetyl, cyanoacetyl or glycyl, lower alkenoyl, for example acryloyl, lower alkynoyl, for example propioloyl, cycloalkylcarbonyl, for example cyclopropylcarbonyl, benzoyl, 4-aminobenzoyl, 4-lower alkanoylaminobenzoyl, for example 4-acetylaminobenzoyl, 4-cyanobenzoyl, 4-nitrobenzoyl or 2,4-dinitrobenzoyl, pyridylcarbonyl, for example nicotinoyl or isonicotinoyl, furoyl, for example 2-furoyl, thienylcarbonyl, for example 2-thienylcarbonyl, hydroxypyrimidylcarbonyl, for example 2,6-dihydroxy-1,3-pyrimid-4-ylcarbonyl, hydroxythiadiazolylcarbonyl, for example 4-hydroxy-1,2,5-thiadiazol-3-ylcarbonyl, tetrazolyl-lower alkanoyl, for example 2-tetrazol-5-ylacetyl or aminothiazolyl-lower alkanoyl, for example 2-(2-amino-1,3-thiazol-4-yl)-acetyl, the acyl group of a semi-ester of carbonic acid, for example lower alkoxycarbonyl, for example methoxycarbonyl or isopropoxycarbonyl, lower alkanoyloxy substituted by carboxy and amino, for example 2-amino-2-carboxyethoxycarbonyl, or benzoyloxycarbonyl, the acyl group of a substituted carbamic acid, for example lower alkylcarbamoyl, for example methylcarbamoyl or anilinocarbonyl, the acyl group of a substituted thio-carbamic acid, for example lower alkylthiocarbamoyl, for example methylthiocarbamoyl, the acyl group of a substituted sulphonic acid, for example lower alkanesulphonyl, for example methanesulphonyl, benzenesulphonyl, 4-nitrobenzenesulphonyl, 2,4-dinitrobenzenesulphonyl, aminobenzenesulphonyl, for example 4-aminobenzenesulphonyl, an acylcarbamoyl group, for example benzoylcarbamoyl or furoylcarbamoyl, an acylthiocarbamoyl group, for example benzoylthiocarbamoyl or furoylthio-carbamoyl, 2-oxo-1-imidazolidinocarbonyl, 4-lower alkyl-2,3-dioxo-1-piperazinocarbonyl, for example 4-ethyl-2,3-dioxo-1-piperazinocarbonyl, and 4-lower alkanesulphonyl-1-piperazinocarbonyl, for example 4-methanesulphonyl-1-piperazinocarbonyl, and $R_6$ represents pyridyl, for example 3- or 4-pyridyl, thienyl, for example 2- or 3-thienyl, furyl, for example 2- or 3-furyl, aminothiazolyl, for example 2-amino-4-thiazolyl, hydroxypyrimidyl, for example 2,6-dihydroxy-1,3-pyrimid-4-yl, aminothiadiazolyl, for example 5-amino-1,2,4-thiadiazol-3-yl, hydroxythiadiazolyl, for example 4-hydroxy-1,2,5-

thiadiazol-3-yl, or aminotriazolyl, for example 5-amino-1,2,4-triazol-3-yl, and to stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

The present invention relates more especially to compounds of the formula I in which *m* represents O, $R_1$ represents hydrogen, lower alkyl, for example methyl, lower alkoxy, for example methoxy, halogen, for example chlorine, or a group $—CH_2—R_2$ wherein $R_2$ represents lower alkanoyloxy, for example acetoxy, carbamoyloxy, triazolylthio, for example 1H-1,2,3-triazol-5-ylthio, tetrazolylthio, for example 1H-tetrazol-5-ylthio, tetrazolylthio substituted by lower alkyl, for example methyl, di-lower alkylamino-lower alkyl, for example 2-dimethylaminoethyl, sulpho-lower alkyl, for example sulphomethyl, carboxy-lower alkyl, for example carboxymethyl, or by carbamoyl, for example 1-methyl-1H-tetrazol-5-ylthio, 1-sulphomethyl-1H-tetrazol-5-ylthio, 1-carboxymethyl-1H-tetrazol-5-ylthio or (1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthio, thiadiazolylthio, for example 1,3,4-thiadiazol-5-ylthio, thiadiazolylthio substituted by lower alkyl, for example methyl, for example 2-methyl-1,3,4-thiadiazol-5-ylthio, 5,6-dioxotetrahydro-as-triazin-3-ylthio substituted by lower alkyl, for example methyl, for example 2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio or 4-methyl-5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio, pyridinio, or pyridinio substituted by hydroxy-lower alkyl, for example hydroxymethyl, carboxy, carboxy-lower alkyl, for example carboxymethyl, halogen, for example chlorine or bromine, or by carbamoyl, for example 3- or 4-hydroxymethylpyridinio, 4-carboxypyridinio, 3- or 4-carboxymethylpyridinio, 3- or 4-chloropyridinio, 3- or 4-bromopyridinio or 3- or 4-carbamoylpyridinio, $R_3$ represents carboxy or carboxy that can be cleaved under physiological conditions, for example acyloxy-lower alkoxycarbonyl, for example lower alkanoyloxy-lower alkoxycarbonyl, for example lower alkanoyloxymethoxycarbonyl or lower alkanoyloxyethoxycarbonyl, for example pivaloyloxymethoxycarbonyl or 2-propionyloxy-ethoxycarbonyl, or lower alkoxycarbonyloxy-lower alkoxycarbonyl, for example 1-ethoxycarbonyl-oxyethoxycarbonyl or tert.-butoxycarbonyloxymethoxycarbonyl, $R_4$ represents hydrogen, $R_5$ represents lower alkyl, for example methyl or ethyl, hydroxy-lower alkyl, for example hydroxymethyl or hydroxy-ethyl, lower alkoxy-lower alkyl, for example methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl, lower alkenyloxy-lower alkyl, for example 2-vinyloxyethyl, halo-lower alkyl, for example chloromethyl or 2-chloroethyl, lower alkylthio-lower alkyl, for example 2-methylthioethyl or 2-ethylthioethyl, carboxy-lower alkyl, for example carboxymethyl or 2-carboxyethyl, carbamoyl-lower alkyl, for example carbamoylmethyl cyano-lower alkyl, for example cyanomethyl or 1-cyano- or 2-cyano-ethyl, or a group of the partial formula A that represents 2-aminoethyl, 2-lower alkylaminoethyl, for example 2-methylaminoethyl or 2-n-hexylaminoethyl, 2-di-lower alkylaminoethyl, for example 2-dimethylaminoethyl or 2-di-n-hexylaminoethyl, 2-sulphoaminoethyl, lower alkanoylaminoethyl, for example 2-formylaminoethyl or 2-acetylaminoethyl, 2-lower alkoxy-lower alkanoylaminoethyl, for example 2-methoxyacetylaminoethyl, 2-halo-lower alkanoylaminoethyl, for example 2-bromoacetyl-aminoethyl, 2-(α-hydroxypropionylamino)-ethyl, 2-glycylaminoethyl, (2-(3-amino-3-carboxypropionylamino)-ethyl, 2-acryloylaminoethyl, 2-propioloylaminoethyl, 2-cyclopropylcarbonyl-aminoethyl, 2-benzoylaminoethyl, 2-(4-aminobenzoylamino)-ethyl, 2-(4-acetylaminobenzoylamino)-ethyl, 2-(4-cyanobenzoylamino)-ethyl, 2-(4-nitrobenzoylamino)-ethyl, 2-(3,4-dinitrobenzoylamino)-ethyl, 2-mandeloylaminoethyl, 2-phenylglycylaminoethyl, 2-nicotinoylaminoethyl, 2-isonicotinoylaminoethyl, 2-(2-furoylamino)-ethyl, 2-(2-thienylcarbonylamino)-ethyl, 2-(2,6-dihydroxy-1,3-pyrimid-4-ylcarbonylamino)-ethyl, 2-(4-hydroxy-1,2,5-thiadiazol-3-ylcarbonylamino)-ethyl, 2-(2-tetrazol-1-ylacetylamino)-ethyl, 2-[2-(2-amino-1,3-thiazol-4-yl)-acetylamino]-ethyl, 2-lower alkoxycarbonylaminoethyl, for example 2-methoxycarbonyl-aminoethyl or 2-isopropoxycarbonylaminoethyl, 2-(2-amino-2-carboxyethoxycarbonylamino)-ethyl, 2-benzoyloxycarbonylaminoethyl, 2-lower alkylcarbamoylaminoethyl, for example 2-methylcarbamoyl-aminoethyl, 2-anilinocarbonylaminoethyl, 2-lower alkylthiocarbamoylaminoethyl, for example 2-methylthiocarbamoylaminoethyl, 2-lower alkanesulphonylaminoethyl, for example 2-methane-sulphonylaminoethyl, 2-halomethanesulphonylaminoethyl, for example 2-difluoromethanesulphonyl-aminoethyl, 2-cyanomethanesulphonylaminoethyl, 2-benzenesulphonylaminoethyl 2-(4-nitro-benzenesulphonylamino)-ethyl, 2-(2,4-dinitrobenzenesulphonylamino)-ethyl, 2-benzoylcarbamoyl-aminoethyl, 2-(2-furoylcarbamoylamino)-ethyl, 2-(2-oxo-1-imidazolidinocarbonylamino)-ethyl, 2-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-ethyl, and 2-(4-methanesulphonyl-1-piperazinocarbonyl-amino)-ethyl, and $R_6$ represents aminothiazolyl, for example 2-amino-4-thiazolyl, aminothiadiazolyl, for example 5-amino-1,2,4-thiadiazol-3-yl, or aminotriazolyl, for example 5-amino-1,2,4-triazol-3-yl, and to stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

The present invention relates first and foremost to compounds of the formula I in which *m* is O, $R_1$ represents hydrogen, lower alkoxy, for example methoxy, halogen, for example chlorine, or a group of the formula $—CH_2—R_2$ wherein $R_2$ represents loweralkanoyloxy, for example acetoxy, carbamoyloxy, tetrazolylthio, for example 1H-tetrazol-5-ylthio, tetrazolylthio substituted by lower alkyl, for example methyl, di-lower alkylamino-lower alkyl, for example 2-dimethylaminoethyl, sulpho-lower alkyl, for example sulphomethyl, or by carboxy-lower alkyl, for example carboxymethyl, for example 1-methyl-1H-tetrazol-5-ylthio, 1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthio, 1-carboxymethyl-1H-tetrazol-5-ylthio, 1-sulphomethyl-1H-tetrazol-5-ylthio, or 1-carboxymethyl-1H-tetrazol-5-ylthio, 5,6-

dioxotetrahydro-as-triazin-3-ylthio, substituted by lower alkyl for example methyl, for example 2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio or 4-methyl-5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio, pyridinio, or pyridinio substituted by hydroxy-lower alkyl, for example hydroxymethyl, carboxy, carboxy-lower alkyl, for example carboxymethyl, halogen, for example chlorine or bromine, or by carbamoyl, for example 3- or 4-hydroxymethylpyridinio, 4-carboxypyridinio, 3- or 4-carboxymethylpyridinio, 3- or 4-chloropyridinio, 3- or 4-bromopyridinio or 3- or 4-carbamoylpyridinio, $R_3$ represents carboxy, lower alkanoyloxy-lower alkoxycarbonyl, for example lower alkanoyloxymethoxycarbonyl or lower alkanoyloxyethoxycarbonyl, for example pivaloyloxymethoxycarbonyl or 2-propionyloxyethoxycarbonyl, or lower alkoxycarbonyloxy-lower alkoxycarbonyl, for example 1-ethoxycarbonyloxyethoxycarbonyl or tert.-butoxycarbonyloxymethoxycarbonyl, $R_4$ represents hydrogen, $R_5$ represents lower alkyl, for example methyl or ethyl, lower alkoxy-lower alkyl, for example methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl, lower alkenyloxy-lower alkyl, for example 2-vinyloxyethyl, halo-lower alkyl, for example chloromethyl or 2-chloroethyl, carboxy-lower alkyl, for example carboxymethyl or 2-carboxyethyl, cyano-lower alkyl, for example cyanomethyl or 1-cyano- or 2-cyano-ethyl, or a group of the partial formula A that represents 2-aminoethyl, 2-lower alkylaminoethyl, for example 2-methylaminoethyl or 2-ethylaminoethyl, 2-di-lower alkylaminoethyl, for example 2-dimethylaminoethyl, 2-sulphoaminoethyl, lower alkanoylaminoethyl, for example 2-formylaminoethyl or 2-acetylaminoethyl, lower alkoxy-lower alkanoylaminoethyl, for example 2-methoxyacetylaminoethyl, cyano-lower alkanoylaminoethyl for example 2-cyanoacetylaminoethyl, lower alkanoylaminoethyl, for example 2-acryloylaminoethyl, lower alkynoylaminoethyl, for example 2-propionylaminoethyl, cycloalkanoylaminoethyl, for example 2-cyclopropanoylaminoethyl, 2-(4-hydroxy-1,2,5-thiadiazol-3-ylcarbonylamino)-ethyl, 2-(2-tetrazol-5-ylacetylamino)-ethyl, 2-[2-(2-amino-1,3-thiazol-4-yl)-acetylamino]-ethyl, 2-lower alkoxycarbonylaminoethyl, for example 2-methoxycarbonylaminoethyl, 2-lower alkanesulphonylaminoethyl, for example 2-methanesulphonylaminoethyl, 2-benzenesulphonylaminoethyl, 2-benzenesulphonylaminoethyl wherein benzene is substituted by nitro or amino, for example 2-(4-nitrobenzenesulphonylamino)-ethyl, 2-(2,4-dinitrobenzenesulphonylamino)-ethyl, 2-(2-oxo-1-imidazolidinocarbonylamino)-ethyl, 2-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-ethyl, or 2-(4-methylsulphonyl-1-piperazinocarbonylamino)-ethyl, and $R_6$ represents aminothiazolyl, for example 2-amino-4-thiazolyl, and to stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

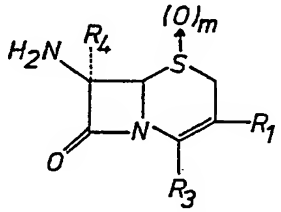
The invention relates most particularly to the compounds of the formula I described in the Examples and their pharmaceutically acceptable salts and to the starting materials and intermediates described therein.

The invention relates above all to the pharmaceutically acceptable salts of compounds of the formula I listed in the experimental report, or their enantiomers.

**Manufacturing process**

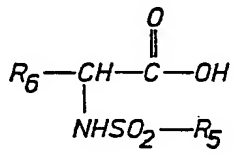
Compounds of the formula I in which the carboxy groups are present in free form or are esterified in physiologically cleavable form, and hydrates and salts of such compounds that have a salt-forming group, are manufactured, for example, as follows:

a) in a compound of the formula



(II)

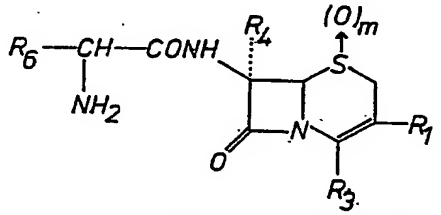
in which $m$, $R_1$, $R_3$ and $R_4$ have the meanings given under formula I and in which a functional group present in $R_1$ is protected and the 7$\beta$-amino group is optionally protected by a group allowing the acylation reaction, the 7$\beta$-amino group is acylated by reaction with an acylating agent that introduces the acyl radical of a carboxylic acid of the formula



(III)

in which $R_5$ and $R_6$ have the meanings given under formula I and in which a functional group present in $R_5$ and/or $R_6$ is in protected form, or

b) in a compound of the formula



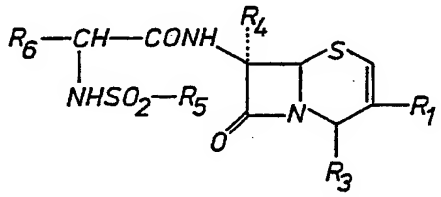
(IV)

in which $m$, $R_1$, $R_3$, $R_4$ and $R_6$ have the meanings given under formula I and in which a functional group present in $R_1$ and/or $R_6$ is protected and the 2-amino group is optionally protected by a group allowing the sulphonylation reaction, the 2-amino group is sulphonylated by reaction with a sulphonylating agent that introduces the $R_5$ sulphonyl radical of a sulphonic acid of the formula

$$R_5—SO_2—OH \qquad (V)$$

in which $R_5$ has the meaning given under formula I and a functional group present in $R_5$ is in protected form, or with a reactive functional acid derivative or a salt thereof, or

c) a 2-cephem compound of the formula



(VI)

in which $R_1$, $R_3$, $R_4$, $R_5$ and $R_6$ have the meanings given under formula I and a functional group present in $R_1$, $R_5$ and/or $R_6$ is optionally in protected form, is isomerised to form the corresponding 3-cephem compound of the formula I, and, if desired, a compound of the formula I obtainable according to the invention is converted into a different compound of the formula I and/or a compound of the formula I obtainable according to the invention in which $m$ represents 0 is converted into a compound of the formula I in which $m$ represents 1 or 2, and/or a compound of the formula I in which $m$ represents 1 or 2 is converted into a compound of the formula I in which $m$ represents 0, and/or any functional group in a compound of the formula I that is present in protected form is converted into the free functional group, and/or a resulting salt is converted into the free compound or into a different salt, and/or a resulting free compound having a salt-forming group is converted into a salt, and/or a resulting mixture of isomeric compounds of the formula I is separated into the individual isomers.

**Process a) (Acylation)**

In a starting material of the formula II, a functional group present in $R_1$, for example a carboxy, amino or hydroxy group, may be protected by a protecting group mentioned hereinbefore, for example a carboxy-, amino- or hydroxy-protecting group.

The 7$\beta$-amino group in a starting material of the formula II is optionally protected by a group allowing the acylation reaction. Such a group is, for example, an organic silyl group, and also an ylidene group which, together with the amino group, forms a Schiff's base. An organic silyl group is, for example, such a group that is also capable of forming a protected carboxy group with a carboxy group $R_3$. It is especially a tri-lower alkylsilyl group, especially trimethylsilyl. In the silylation reaction for the protection of a 4-carboxy group in a starting material of the formula II, if an excess of the silylating agent is used, the amino group may likewise be silylated. An ylidene group is especially a 1-aryl-lower alkylidene group, especially a 1-arylmethylene group, wherein aryl represents especially a carbocyclic, primarily a monocyclic, aryl, radical for example phenyl optionally substituted by lower alkyl, hydroxy, lower alkoxy and/or nitro.

An acylating agent that introduces the acyl radical of a carboxylic acid of the formula III may be the carboxylic acid of the formula III itself or a reactive functional derivative or salt thereof.

In a starting material of the formula III, any functional group present in $R_5$ and/or $R_6$, for example a carboxy group, that is not to participate in the acylation reaction, or an amino or hydroxy group, may be protected by a protecting group mentioned hereinbefore, for example by a carboxy-, amino- or hydroxy-protecting group.

In a starting material in the formula III, any amino group present may also be protected in ionic form, for example in the form of an acid addition salt, which is formed, for example, with a strong inorganic acid, for example a hydrohalic acid, for example hydrochloric acid, or sulphuric acid, or with an organic acid, for example $p$-toluenesulphonic acid.

If a free acid of the formula III is used for acylation, the reaction is customarily carried out in the presence of suitable condensation agents, such as carbodiimides, for example N,N'-diethyl-, N,N'-dipropyl, N,N'-dicyclohexyl or N-ethyl-N'-3-dimethylaminopropyl carbodiimide, suitable carbonyl compounds, for example carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium 3'-sulphonate or 2-tert.-butyl-5-methyl-1,2-oxazolium perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline.

The condensation reaction is preferably carried out in an anhydrous reaction medium, preferably in the presence of a solvent, for example methylene chloride, dimethylformamide, acetonitrile or tetrahydrofuran, optionally while cooling or heating, for example in a temperature range of from approximately —40°C to approximately +100°C, preferably from approximately —20° to approximately +50°C, and optionally under an inert gas atmosphere, for example a nitrogen atmosphere.

A reactive, that is to say forming the carboxamide function, functional derivative of a carboxylic acid of the formula III is especially an anhydride of the carboxylic acid of the formula III, preferably a mixed anhydride. A mixed anhydride is formed, for example, by condensation with a different acid, for example an inorganic acid, for example a hydrohalic acid, and is, for example, the corresponding carboxylic acid halide, for example the carboxylic acid chloride or bromide. A mixed anhydride may also be formed by condensation with hydrazoic acid and is, for example, the carboxylic acid azide. Other inorganic acids that are suitable for the formation of the mixed anhydride are phosphorus-containing acids, for example phosphoric acid, diethylphosphoric acid and phosphorous acids, sulphur-containing acids, for example sulphuric acid, or hydrocyanic acid. A reactive functional derivative of a carboxylic acid of the formula III may also be formed by condensation with an organic carboxylic acid, for example with a lower alkanecarboxylic acid that is unsubstituted or substituted by halogen, for example fluorine or chlorine, for example pivalic acid or trifluoroacetic acid, with a lower alkyl semi-ester of carbonic acid, for example the ethyl or isobutyl semiester of carbonic acid, or with an organic, for example aliphatic or aromatic, sulphonic acid, for example methanesulphonic acid, or *p*-toluenesulphonic acid.

A reactive functional derivative of a carboxylic acid of the formula III may likewise be an activated ester of the carboxylic acid of the formula III, which is formed, for example, by condensation with a vinylogous alcohol, that is to say with an enol, for example a vinylogous lower alkenol, or an iminomethyl ester halide, for example dimethyliminomethyl ester chloride, manufactured from the carboxylic acid of the formula III and, for example, dimethyl-(1-chloroethylidene)-iminium chloride of the formula $[(CH_3)_2N^{\oplus}=C(Cl)CH_3]Cl^{\ominus}$, which can in turn be obtained, for example, from N,N-dimethylacetamide and phosgene or oxalyl chloride, or an aryl ester, for example a phenyl ester substituted by halogen, for example chlorine, and/or by nitro, for example a pentachlorophenyl 4-nitrophenyl or 2,3-dinitrophenyl ester, an N-heteroaromatic ester, for example an N-benzotriazole ester, or an N-diacylimino ester, for example an N-succinylimino or N-phthalylimino ester.

The acylation with a reactive functional derivative of the carboxylic acid of the formula III, for example with a corresponding anhydride, especially an acid halide, is preferably carried out in the presence of one of the mentioned condensation agents, for example a carbodiimide, for example dicyclohexyl carbodiimide, or a suitable base. A suitable base is, for example, an amine, for example a tertiary amine, for example tri-lower alkylamine, for example trimethylamine, triethylamine or ethyl diisopropylamine, or N,N-di-lower alkylaniline, for example N,N-dimethylaniline, or a cyclic tertiary amine, for example an N-lower alkylated morpholine, for example N-methylmorpholine, or is, for example, a base of the pyridine type, for example pyridine. A suitable base is also an inorganic base, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate, for example sodium, potassium or calcium hydroxide, carbonate or bicarbonate, or is an oxirane, for example a 1,2-lower alkylene oxide, such as ethylene oxide or propylene oxide.

The acylation with a reactive functional derivative of the carboxylic acid of the formula III is preferably carried out in an inert, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example a formamide, for example dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, carbon tetrachloride or chlorobenzene, a ketone, for example acetone, a cyclic ether, for example tetrahydrofuran, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or mixtures thereof, optionally at reduced or elevated temperature, for example in a temperature range of from approximately —40°C to approximately +100°C, preferably from approximately —10°C to approximately +50°C, and optionally under an inert gas atmosphere, for example a nitrogen atmosphere.

When using a suitable reactive functional derivative of the acid of the formula III the acylation of a compound of the formula II can also be effected in the presence of a suitable acylase. Such acylases are known and can be formed by a number of micro-organisms, for example by acetobacter, such as *Acetobacter aurantium*, achromobacter, such as *Achromobacter aeris*, aeromonas, such as *Aeromonas hydrophila*, or bacillus, such as *Bacillus megaterium 400*. In such an enzymatic acylation there is used as the reactive functional derivative especially an amide, ester or thioester, such as a lower alkyl ester, for example a methyl or ethyl ester, of the carboxylic acid of the formula III. Acylation of this kind is usually carried out in a nutrient medium containing the corresponding micro-organism, in a filtrate of the culture broth or, optionally after isolation of the acylase, including after adsorption on a carrier, in

an aqueous medium optionally containing a buffer, for example in a temperature range of from approximately +20°C to approximately +40°C, preferably at approximately +37°C.

A reactive functional derivative of an acid of the formula III used in the acylation reaction may, if desired, be formed *in situ*. Thus, for example, a mixed anhydride can be manufactured *in situ* by reacting an acid of the formula III in which functional groups are optionally protected, or a suitable salt thereof, for example an ammonium salt, which is formed, for example, with an organic base, such as pyridine or 4-methylmorpholine, or a metal salt, for example an alkali metal salt, for example a sodium salt, with a suitable derivative of a different acid, for example an acid halide, of a lower alkanecarboxylic acid that is unsubstituted or substituted by halogen, for example chlorine, for example trichloroacetyl chloride, with a semi-ester of a carbonic acid semihalide, for example chloroformic acid ethyl ester or isobutyl ester, or with a halide of a di-lower alkylphosphoric acid, for example diethyl phosphorobromidate, which can be formed by reacting triethyl phosphite with bromine. The mixed anhydride so obtained can be used in the acylation reaction without being isolated.

**Process b) (Sulphonylation)**

In a starting material of the formula IV a functional group present in $R_1$ and/or $R_6$, for example a carboxy, amino or hydroxy group, may be protected by a protecting group mentioned hereinbefore, for example by a carboxy-, amino- or hydroxy-protecting group.

The 2-amino group in a starting material of the formula IV is optionally protected by a group allowing the sulphonylation reaction. Such a group is, for example, an organic silyl group, for example a tri-lower alkylsilyl group, for example trimethylsilyl, or an ylidene group which, together with the amino group, forms a Schiff's base, and is the same group as that optionally substituting the 7$\beta$-amino group in a starting material of the formula II allowing the acylation reaction according to process a)

A sulphonylating agent that introduces the $R_5$ sulphonyl radical of a sulphonic acid of the formula V may be the sulphonic acid of the formula V itself or a reactive functional derivative thereof.

In a starting material of the formula V, a functional group present in $R_5$, for example a carboxy group, an amino or hydroxy group, or a sulphonyl group that is not to participitate in the acylation reaction, may be protected by a protecting group mentioned hereinbefore, for example a carboxy-, amino-, hydroxy- or sulphonyl-protecting group.

In a starting material of the formula V, an amino group present may be protected in ionic form in the same manner as an amino group present in a starting material of the formula III, for example in the form of an acid addition salt, for example a hydrochloride.

If a free sulphonic acid of the formula V is used in the sulphonylation, the sulphonylation is customarily carried out in the presence of the same condensation agent as that used in the acylation of the 7$\beta$-amino group in a compound of the formula II with a free carboxylic acid of the formula III in accordance with process a), for example in the presence of a carbodiimide, for example N,N'-dicyclohexyl carbodiimide.

In the sulphonylation with a free sulphonic acid of the formula V, the same solvents are used and the same reaction conditions are observed as in the acylation with a free carboxylic acid of the formula III in accordance with process a).

A reactive, that is to say forming the sulphonamide function, functional derivative of a sulphonic acid of the formula V is especially an anhydride of the sulphonic acid of the formula V, preferably a mixed anhydride. A mixed anhydride is formed, for example, by condensation with an inorganic acid, for example a hydrohalic acid, and is, for example, the corresponding sulphonic acid halide, for example the sulphonic acid chloride or bromide. Other inorganic acids that are suitable for the formation of the mixed anhydride are phosphorus-containing acids, for example phosphoric acid, diethylphosphoric acid or phosphorous acid, or sulphur-containing acids, for example sulphuric acid. A reactive functional derivative of a sulphonic acid of the formula V may also be formed by condensation with an organic carboxylic acid, for example with a lower alkanecarboxylic acid that is unsubstituted or substituted by halogen, for example fluorine or chlorine, for example pivalic acid or trifluoroacetic acid, with a lower alkyl semi-ester of carbonic acid, for example the ethyl or isobutyl semi-ester of carbonic acid, or with a different sulphonic acid, for example an aliphatic or aromatic sulphonic acid, for example methanesulphonic acid or *p*-toluenesulphonic acid.

A reactive functional derivative of a sulphonic acid of the formula V may likewise be an activated ester of the sulphonic acid of the formula V. An activated ester is formed, for example, by condensation with a vinylogous alcohol, that is to say with an enol, for example, a vinylogous lower alkenol, or is, for example, a phenyl ester substituted by halogen, for example chlorine, and/or by nitro, for example a pentachlorophenyl, 4-nitrophenyl or 2,3-dinitrophenyl ester, an N-heteroaromatic ester, for example an N-benzotriazole ester, or is an N-diacylimino ester, for example an N-succinylimino ester or a phthalylimino ester.

In the sulphonylation with a reactive functional derivative of a sulphonic acid of the formula V, the same solvents are used and the same reaction conditions observed as in the acylation with a reactive functional derivative of a carboxylic acid of the formula III in accordance with process a).

**Process c) (Isomerisation)**

In a 2-cephem starting material of the formula VI, the optionally protected 4-carboxy group is preferably in the $\alpha$-configuration.

A 2-cephem compound of the formula VI may be isomerised by treatment with a basic agent and isolation of the corresponding 3-cephem compound. As the basic agent there may be used an organic, nitrogen-containing base, especially a tertiary heterocyclic base of aromatic character, especially a base of the pyridine type, for example pyridine, picoline, collidine or lutidine, and also quinoline, a tertiary aromatic base, for example of the aniline type, for example an N,N-di-lower alkylaniline, for example N,N-dimethylaniline or N,N-diethylaniline, or a tertiary aliphatic, azacycloaliphatic or araliphatic base, for example a tri-lower alkylamine, for example trimethylamine or N,N-diisopropyl-N-ethylamine, an N-lower alkylazacycloalkane, for example N-methylpiperidine, or an N-phenyl-lower alkyl-N,N-di-lower alkylamine, for example N-benzyl-N,N-dimethylamine, and also a mixture of such basic agents, for example a mixture of a base of the pyridine type and a tri-lower alkylamine, for example pyridine and triethylamine. Furthermore, an inorganic or organic, basic salt, especially a basic salt of a medium-strength to strong base with a weak acid, for example an alkali metal or ammonium salt or a lower alkanecarboxylic acid, for example sodium acetate, triethylammonium acetate or N-methylpiperidine acetate, and other analogous bases or mixtures of such basic agents can also be used.

The isomerisation of a 2-cephem compound of the formula VI with a basic agent is preferably carried out in an anhydrous medium, in the presence or absence of a solvent, such as an optionally halogenated, for example chlorinated, aliphatic, cycloaliphatic or aromatic hydrocarbon, or a solvent mixture, it being possible for the base used as isomerising agent which is liquid under the reaction conditions to serve simultaneously as the solvent. The operation is carried out optionally while cooling or heating, preferably in a temperature range of from approximately −30°C to approximately +100°C, and optionally under an inert gas atmosphere, for example a nitrogen atmosphere.

A 3-cephem compound of the formula I obtainable in this manner can be separated from 2-cephem starting material of the formula VI which may still be present in a manner known *per se*, for example by adsorption chromatography and/or crystallisation.

The isomerisation of a 2-cephem compound of the formula VI to form the corresponding 3-cephem compound of the formula I is preferably carried out by oxidising the 2-cephem compound of the formula VI in the 1-position using a suitable oxidising agent and, if desired, separating an isomeric mixture of the 1-oxides which may be obtained and reducing a resulting 1-oxide of the 3-cephem compound of the formula I in which $m$ represents 1 to the 3-cephem compound in which $m$ represents 0.

As oxidising agents for the oxidation of the sulphur atom in the 1-position of a 2-cephem compound of the formula VI there are suitable inorganic peracids that have a reduction potential of at least +1.5 volts and consist of non-metallic elements, organic peracids or mixtures consisting of hydrogen peroxide and acids, especially organic carboxylic acids, having a dissociation constant of at least $10^{-5}$. Suitable inorganic peracids are, for example, periodic acid and persulphuric acid. Organic peracids are, for example, percarboxylic and persulphonic acids which may be added in the form of the peracid or may be formed *in situ* by using at least one equivalent of hydrogen peroxide and a carboxylic acid. In the case of *in situ* formation of the peracid, it is expedient to use a large excess of the carboxylic acid, for example acetic acid, as solvent. Suitable organic peracids are preferably performic acid, peracetic acid, trifluoroperacetic acid, permaleic acid, perbenzoic acid, 3-chloroperbenzoic acid, monoperphthalic acid or *p*-toluenepersulphonic acid.

The oxidation can likewise be effected using hydrogen peroxide with catalytic amounts of an acid having a dissociation constant of at least $10^{-5}$, it being possible to use low concentrations, for example 1—2% and lower, or alternatively relatively large amounts of the acid in question. In this case, the oxidative effectiveness of the mixture depends chiefly on the strength of the acid. Suitable mixtures are, for example, hydrogen peroxide with acetic acid, perchloric acid or trifluoroacetic acid.

The above oxidation may be carried out in the presence of suitable acidic catalysts. Thus, for example, the oxidation with a percarboxylic acid can be catalysed by the presence of an acid having a dissociation constant of at least $10^{-5}$, the catalytic effectiveness of this acid being dependent on its acid strength. Acids suitable as catalysts are, for example, acetic acid, perchloric acid and trifluoroacetic acid. Usually, at least equimolar amounts of the oxidising agent, and preferably a slight excess of from approximately 10% to approximately 20%, are used, it being possible alternatively to use relatively large excesses, that is to say up to 10 times the amount or more of the oxidising agent. The oxidation is carried out under mild conditions, for example at temperatures of from approximately −50°C to approximately +100°C, preferably from approximately −10°C to approximately +40°C.

The reduction of a 1-oxide of the 3-cephem compound, that is to say 3-cephem compound of the formula I in which $m$ represents 0, can be carried out in a manner known *per se* by treatment with a suitable reducing agent, if necessary in the presence of an activating agent. Suitable reducing agents are, for example: tin, iron, copper or manganese cations having a reducing action, which are used in the form of their salts, for example in the form of tin(II) chloride, acetate or formate, iron(II) chloride, sulphate or oxalate, or ammonium iron sulphate, copper(I) chloride or oxide, or manganese(II) chloride,

sulphate, acetate or oxide, or in the form of organic or inorganic complexes, for example with ethylenediaminetetraacetic acid or nitrilotriacetic acid; dithionite, iodide or iron(II) cyanide anions having a reducing action, which are used in the form of their inorganic or organic salts, for example in the form of alkali metal dithionite, iodide or iron(II) cyanide, for example sodium or potassium dithionite, sodium or potassium iodide or sodium or potassium iron(II) cyanide; hydriodic acid; trivalent inorganic or organic phosphorus compounds having a reducing action, such as phosphines, also esters, amides and halides of phosphonous, phosphinous, or phosphorous acid, and also phosphorus-sulphur compounds corresponding to these phosphorus-oxygen compounds, wherein in these compounds organic radicals are especially aliphatic, aromatic or araliphatic radicals, for example optionally substituted lower alkyl, phenyl or phenyl-lower alkyl, for example triphenylphosphine, diphenylphosphonous acid methyl ester, diphenylchlorophosphine, phenyldichlorophosphine, benzenephosphonous acid dimethyl ester, phosphorous acid triphenyl ester, phosphorous acid trimethyl ester, phosphorus trichloride, phosphorus tribromide, also phosphorous acid triphenyl ester-halogen adducts, for example chlorine or bromine adducts, in which the phenyl radicals are optionally substituted by lower alkyl, for example methyl, lower alkoxy, for example methoxy, or by halogen, for example chlorine, *etc.*; halosilane compounds having a reducing action that have at least one hydrogen atom bonded to the silicon atom and which may contain, apart from halogen, such as chlorine, bromine or iodine, also organic radicals, such as aliphatic or aromatic groups, for example optionally substituted lower alkyl or phenyl, for example diphenylchlorosilane or dimethylchlorosilane, and also halosilane compounds in which all the hydrogen atoms are replaced by organic radicals, such as tri-lower alkylhalosilane, for example trimethylchlorosilane or trimethyliodosilane, *etc.*; or quaternary chloromethylene-iminium salts having a reducing action, especially chlorides or bromides, in which the iminium group is substituted by one bivalent or two monovalent organic radicals, such as optionally substituted lower alkylene or lower alkyl, such as N-chloromethylene-N,N-dimethyl-iminium chloride or N-chloromethylene-pyrrolidinium chloride; or complex metal hydrides, such as sodium borohydride, in the presence of suitable activating agents, such as cobalt(II) chloride, and also borane dichloride.

Activating agents are used together with those reducing agents which have no, or only slight, Lewis acid properties. These are used especially together with dithionite, iodide or iron(II) cyanide salts and non-halogen-containing trivalent phosphorus reducing agents and are especially organic carboxylic and sulphonic acid halides, for example phosgene, oxalyl chloride, acetyl chloride or bromide or chloroacetyl chloride.

The reduction is preferably carried out in the presence of solvents or mixtures thereof, the choice of which is determined primarily by the solubility of the starting materials and the chosen reducing agent, for example optionally substituted, for example halogenated or nitrated, aliphatic, cycloaliphatic, aromatic or araliphatic hydrocarbons, for example benzene, methylene chloride, chloroform or nitromethane, suitable acid derivatives, such as lower alkanecarboxylic acid esters or nitriles, for example ethyl acetate or acetonitrile, or amides of inorganic or organic acids, for example dimethylformamide or hexamethylphosphoramide, ethers, for example diethyl ether, tetrahydrofuran or dioxan, ketones, for example acetone, or sulphones, especially aliphatic sulphones, for example dimethylsulphone or tetramethylenesulphone, *etc.*, together with the chemical reducing agents, these solvents preferably containing no water.

The reaction is usually carried out at temperatures of from approximately −20° to approximately 100°C, it being possible when using very reactive reducing agents or activating agents, to carry out the reaction also at lower temperatures, and optionally under an inert gas atmosphere, for example a nitrogen atmosphere.

**Subsequent operations**

In a resulting compound of the formula I, in a customary manner known *per se*, functional groups that are not yet protected can be protected, or any protecting group present can be exchanged for another protecting group, for example by removing the protecting group present and introducing the desired other protecting group.

**$R_1$ conversions**

In a resulting compound of the formua I in which functional groups are optionally protected, in a manner known *per se*, a group $R_1$ can be replaced by a different radical $R_1$ or converted into a different radical $R_1$. It is possible, for example, in a compound of the formula I in which $R_1$ represents a group of the formula $—CH_2—R_2$ and $R_2$ represents, for example, a radical that can be replaced by nucleophilic substituents, or in a salt thereof, to replace such a radical, $R_2$ by an etherified mercapto group $R_2$, for example a heterocyclylmercapto group, or an esterified mercapto group $R_2$ by treatment with a mercaptan, for example a heterocyclylmercaptan, or a thiocarboxylic acid compound, respectively.

A suitable radical that can be replaced by nucleophilic substituents, for example by an etherified mercapto group, is, for example, a hydroxy group esterified by a lower aliphatic carboxylic acid. Such an esterified hydroxy group is especially acetoxy or acetoacetoxy.

The reaction of such a compound of the formula I with a suitable mercaptan, for example a heterocyclylmercaptan, can be carried out under acidic, neutral or weakly basic conditions. In the case

of acidic conditions the reaction is carried out in the presence of concentrated sulphuric acid, which is optionally diluted by an inorganic solvent, for example polyphosphoric acid. In the case of neutral or weakly basic conditions the reaction is carried out in the presence of water and optionally a water-miscible organic solvent.

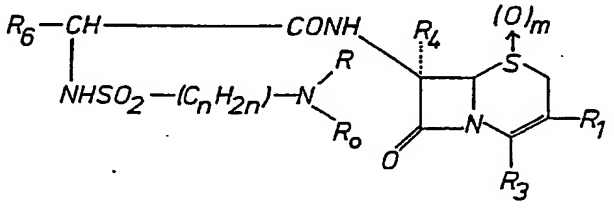
The basic conditions can be established, for example, by the addition of an inorganic base, such as an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate, for example by the addition of sodium potassium or calcium hydroxide, carbonate or bicarbonate. There may be used as organic solvents, for example, water-miscible alcohols, for example lower alkanols, such as methanol or ethanol, ketones, for example lower alkanones, such as acetone, amides, for example lower alkanecarboxylic acid amides, for example dimethylformamide, or nitriles, for example lower alkanoic acid nitriles, for example acetonitrile.

In a compound of the formula I in which $R_1$ represents a group of the formula $—CH_2—R_2$ wherein $R_2$ represents free hydroxy, the free hydroxy group can be esterified by the acyl radical of an optionally N-substituted carbamic acid. The esterification of the free hydroxy group with an isocyanate compound, for example halosulphonyl isocyanate, for example chlorosulphonyl isocyanate, or with a carbamic acid halide, for example carbamic acid chloride, results in N-unsubstituted 3-carbamoyloxymethyl cephalosporins of the formula I. The esterification of the free hydroxy group with an N-substituted isocyanate compound or with an N-mono- or N,N-di-substituted carbamic acid compound, for example a correspondingly substituted carbamic acid halide, for example an N-mono- or N,N-di-substituted carbamic acid chloride, results in N-mono- or N,N-di-substituted 3-carbamoyloxymethylcephalosporins of the formula I. The operation is customarily carried out in the presence of a solvent or diluent and, if necessary, while cooling or heating, in a closed vessel and optionally under an inert gas atmosphere, for example a nitrogen atmosphere. The compounds of the formula I in which $R_1$ represents a group of the formula $—CH_2—R_2$ wherein $R_2$ represents free hydroxy can be obtained from a compound of the formula I by removing the acetyl radical from an acetoxy group $R_2$, for example by hydrolysis in a weakly basic medium, for example in an aqueous sodium hydroxide solution at pH 9—10, or by treatment with a suitable esterase, such as a corresponding enzyme selected from *Rhizobium tritolii, Rhizobium lupinii, Rhizobium japonicum* or *Bacillus subtilis*, or a suitable citrus esterase, for example from orange peel.

Furthermore, a compound of the formula I in which $R_1$ represents a group $—CH_2—R_2$, $R_2$ representing, for example, the above-defined radical, that can be replaced by nucleophilic substituents, for example acetoxy or acetoacetoxy, can be reacted with an organic base, especially with a tertiary, nitrogen-containing base, for example a tertiary, aliphatic amine, or preferably a tertiary heterocyclic, aromatic nitrogen base, for example pyridine or pyrimidine having the substituents mentioned hereinbefore, under neutral or weakly acidic conditions, preferably at a pH value of approximately 6.5, in the presence of water and optionally in a water-miscible organic solvent. There are thus obtained compounds of the formula I in which $R_1$ represents the radical of the formula $—CH_2—R_2$ and $R_2$ represents an ammonio group defined hereinbefore. Weakly acidic conditions can be established by the addition of a suitable organic or inorganic acid, for example acetic acid, hydrochloric acid, phosphoric acid or sulphuric acid. As organic solvents there may be used, for example, the water-miscible solvents mentioned above. In order to increase the yield, salts may be added to the reaction mixture, for example alkali metal salts, such as sodium or, especially, potassium salts, of inorganic acids, such as hydrohalic acids, for example hydrochloric and, especially, hydriodic acid, and of thiocyanic acid, or of organic acids, such as lower alkanecarboxylic acids, for example acetic acid. Suitable salts are, for example, sodium iodide, potassium iodide and potassium thiocyanate. It is also possible to use for this purpose salts of certain anion exchangers, for example liquid ion exchangers in salt form, such as, for example, Amberlite LA-1 (liquid secondary amines having a molecular weight of from 351 to 393; oil-soluble and water-insoluble; meq./g=2.5—2.7, for example in acetate form), with acids, for example acetic acid.

**Acylation of the free amino group**

In a resulting compound of the formula



(I')

in which *m*, $R_1$, $R_3$, $R_4$ and $R_6$ have the meanings given under formula I, *n* is an integer from 1 to 4, $R_o$ represents hydrogen or lower alkyl and R represents hydrogen, the amino group can be substituted in a manner known *per se* by sulpho, which is optionally present in salt form, or by an acyl group.

This substitution can be effected, for example, by reaction with an acylating agent that introduces the sulpho radical R or an acylating agent that introduces the corresponding acyl radical R. The carboxy group $R_3$, and any functional group present in $R_1$ and $R_6$, for example an amino or hydroxy group, may be protected by the protecting groups mentioned hereinbefore.

If the amino group is substituted by a sulpho radical R, there is used as acylating agent, for example, a sulphur trioxide-tert.-amine complex, for example the sulphur trioxide-triethylamine complex.

If the amino group is substituted by an acyl group $R^a$—CO—, there is used as acylating agent, for example, the carboxylic acid $R^a$—CO—OH or a reactive functional derivative thereof. A reactive functional derivative of the carboxylic acid $R^a$—CO—OH is, for example, a mixed anhydride or an activated ester, which can be obtained in the manner described under process a) (acylation) by condensation of the carboxylic acid $R^a$—CO—OH with an inorganic acid, a carboxylic acid, a semi-ester of carbonic acid or with a sulphonic acid or by condensation with a vinylogous alcohol *etc.*

If the amino group is substituted by an acyl group $R^a$—$SO_2$—, there is used as acylating agent, for example, the sulphonic acid $R^a$—$SO_2$—OH or a reactive functional derivative thereof. A reactive functional derivative of the sulphonic acid $R^a$—$SO_2$—OH is, for example, a mixed anhydride or an activated ester, which can be obtained in the manner described under process b) (sulphonylation) by condensation of the sulphonic acid $R^a$—$SO_2$—OH with an inorganic acid, a carboxylic acid, a semi-ester of carbonic acid or with a different sulphonic acid or by condensation with a vinylogous alcohol.

In the acylation of the free amino group with a free carboxylic acid of the formula $R^a$—CO—OH or with a free sulphonic acid of the formula $R^a$—$SO_2$—OH, the same condensation agents, for example carbodiimides, and the same solvents are used and the same reaction conditions are observed as in the acylation according to process a).

In the acylation of the free amino group with one of the reactive functional derivatives described hereinbefore, the same solvents are used and the same reaction conditions are observed as in the acylation with a reactive functional derivative of a carboxylic acid of the formula III in accordance with process a).

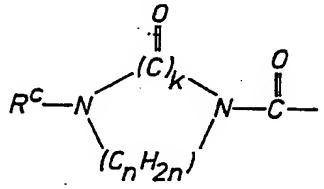
A reactive functional derivative of this type is, for example, an anhydride, for example a mixed anhydride, for example a mixed anhydride with an organic acid, for example a hydrohalic acid, for example hydrogen chloride, for example the acyl chloride, or, in the case of carbamic acid or thiocarbamic acid, an internal anhydride, for example a cyanate or thiocyanate.

If the amino group is substituted by an acyl group of the partial formula

$$R^a\text{—O—CO—},\quad (R^a)R^bN\text{—CO—},\quad (R^a)R^bN\text{—CS—},$$

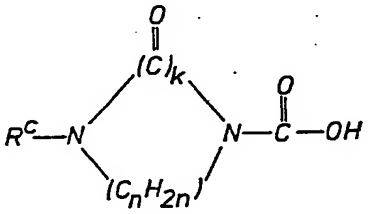
$$(R^a)R^bN\text{—}SO_2\text{—},\quad (R^a\text{—CO—})R^bN\text{—CO—},\quad (R^a\text{—CO—})R^bN\text{—CS—}$$

or



(B)

there is used as acylating agent a reactive functional derivative of the corresponding carbonic acid semiester, of the corresponding carbamic acid, thiocarbamic acid, amidosulphonic acid, acylcarbamic acid or acylthiocarbamic acid, or a reactive functional derivative of the carboxylic acid of the formula



**Alkylation of the amino group**

In a resulting compound of the formula (I') in which *m*, $R_1$, $R_3$, $R_4$ and $R_6$ have the meanings given under formula I, *n* is an integer from 1 to 4, $R_o$ represents hydrogen and R represents hydrogen, sulpho optionally present in salt form, or an acyl group, the amino group can be alkylated in a manner known *per se* by a suitable alkylating agent that introduces the lower alkyl radical $R_o$ or R, for example an alkyl halide, for example methyl bromide.

**Conversion to the 1-oxide, 1-dioxide and 1-sulphide**

A compound of the formula I in which the index *m* is 0 can be converted by the oxidising agents described under process c) into the corresponding 1-oxide in which the index *m* is 1.

1-oxides of the formula I that are in the β-configuration can be produced in a manner known *per se* according to the process known from German Offenlegungsschrift 30 13 996, that is to say by oxidation of a 1-sulphide of the formula I or VI (*m*=0) with a percarboxylic acid, for example peracetic acid or *m*-chloroperbenzoic acid.

1-oxides of the formula I that are in the α- or β-configuration can be produced in a manner known *per se* according to the process known from German Offenlegungsschrift 30 13 996, that is to say by oxidation of a 1-sulphide of the formula II in which the 7β-amino group is protected, for example, by ylidene groups which, together with the amino group, form a Schiff's base, with a percarboxylic acid, for example *m*-chloroperbenzoic acid, chromatographic separation of the resulting α- and β-1-oxides of the formula II and subsequent acylation with a carboxylic acid of the formula III.

A compound of the formula I in which the index *m* is 0 or 1 can be converted into the corresponding 1-dioxide in which *m* is 2 by reaction with oxidising agents that convert sulphide or sulphoxide groups into sulphone groups.

Such oxidising agents are especially hydrogen peroxide, organic peracids, especially aliphatic percarboxylic acids, for example peracetic acid, perbenzoic acid, chloroperbenzoic acid, for example *m*-chloroperbenzoic acid, or monoperphthalic acid, oxidising inorganic acids or their salts, for example nitric acid, chromic acid, potassium permanganate, or alkali metal hypochlorite, for example sodium hypochlorite, or anodic oxidation may be used. The oxidation is preferably carried out in a suitable inert solvent, for example a halogenated hydrocarbon, for example methylene chloride, chloroform or carbon tetrachloride, an alcohol, for example methanol or ethanol, a ketone, for example acetone, an ether, for example diethyl ether, dioxan or tetrahydrofuran, an amide, for example dimethylformamide, a sulphone, for example dimethylsulphone, a liquid organic carboxylic acid, for example acetic acid, or in water or a mixture of these solvents, especially an aqueous mixture, for example aqueous acetic acid, at room temperature, or while cooling or gently heating, that is to say at from approximately −20°C to approximately +90°C, preferably at from approximately −20°C to approximately +30°C. The oxidation can also be carried out in stages by first oxidising at low temperature, that is to say at from approximately −20°C to approximately 0°C, to the sulphoxide stage, which is optionally isolated, then in a second stage, oxidising the sulphoxide to the sulphone, that is to say to the 1,1-dioxide of the formula I, preferably at higher temperature, for example at room temperature.

For working up, excess oxidising agent which may still be present can be eliminated by reduction, especially by treatment with a reducing agent, such as a thiosulphate, for example sodium thiosulphate.

A 1-oxide of the formula I in which the index *m* is 1, and a 1-dioxide in which the index *m* is 2, can be converted by the reducing agents described under process c) into the corresponding 1-sulphide in which the index *m* is 0.

**Removal of protecting groups**

In a resulting compound of the formula I in which one or more functional groups are protected, these, for example, protected carboxy, amino, hydroxy and/or sulpho groups, may be freed in a manner known *per se*, either in stages or simultaneously, by means of solvolysis, especially hydrolysis, alcoholysis or acidolysis or by means of reduction, especially hydrogenolysis.

A protected carboxy group may be freed in a manner known *per se*, and depending on the nature of the protecting groups, by various methods, but preferably by means of solvolysis or reduction.

Thus, tert.-lower alkoxycarbonyl, or lower alkoxycarbonyl substituted in the 2-position by an organic silyl group or in the 1-position by lower alkoxy or lower alkylthio, or optionally substituted diphenylmethoxycarbonyl can be converted into free carboxy, for example by treatment with a suitable acid, such as formic acid or trifluoroacetic acid, optionally with the addition of a nucleophilic compound, such as phenol, anisole or ethylene thioglycol. Suitably substituted benzyloxycarbonyl, such as 4-nitrobenzyloxycarbonyl, can be converted into free carboxy by means of chemical reduction, for example by treatment with an alkali metal dithionite, for example sodium dithionite, or with a reducing metal, for example zinc, or a reducing metal salt, such as a chromium(II) salt, for example chromium(II) chloride, usually in the presence of an agent that yields hydrogen ions and that, together with the metal or metal salt, is capable of producing nascent hydrogen, such as an acid, especially a suitable carboxylic acid, such as a lower alkanecarboxylic acid optionally substituted, for example, by hydroxy, for example acetic acid, formic acid, glycolic acid, diphenylglycolic acid, lactic acid, mandelic acid, 4-chloromandelic acid or tartaric acid, or of an alcohol or thiol, water preferably being added. By treatment with a reducing metal or metal salt, as described above it is also possible to convert 2-halo-lower alkoxycarbonyl (optionally after conversion of a 2-bromo-lower alkoxycarbonyl group into a corresponding 2-iodo-lower alkoxycarbonyl group) or aroylmethoxycarbonyl into free carboxy, it being possible to cleave aroylmethoxycarbonyl also by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate or sodium iodide. Substituted 2-silylethoxycarbonyl can also be converted into free carboxy by treatment with a salt of hydrofluoric acid yielding the fluoride anion, such as an alkali metal fluoride, for example

sodium or potassium fluoride, in the presence of a macrocyclic polyether ("Crown ether"), or with a fluoride of an organic quaternary base, such as tetra-lower alkylammonium fluoride or tri-lower alkylarylammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic polar solvent, such as dimethyl sulphoxide or N,N-dimethylacetamide. Carboxy esterified by an organic silyl group, such as tri-lower alkylsilyl, for example trimethylsilyl, can customarily be freed by solvolysis, for example by treatment with water, an alcohol or an acid.

A protected amino group may be freed in a manner known *per se* and, depending on the nature of the protecting groups, by various methods, but preferably by solvolysis or reduction 2-halo-lower alkoxycarbonylamino, optionally after conversion of a 2-bromo-lower alkoxycarbonylamino group into a 2-iodo-lower alkoxycarbonylamino group, aroylmethoxycarbonylamino or 4-nitrobenzyloxy-carbonylamino can be cleaved, for example, by treatment with a suitable chemical reducing agent, such as zinc in the presence of a suitable carboxylic acid, such as aqueous acetic acid. Aroylmethoxy-carbonylamino can also be cleaved by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate, and 4-nitrobenzyloxycarbonylamino also by treatment with an alkali metal dithionite, for example sodium dithionite. Optionally substituted diphenylmethoxy-carbonylamino, tert.-lower alkoxycarbonylamino or 2-tri-substituted silylethoxycarbonylamino can be cleaved by treatment with a suitable acid, for example formic acid or trifluoroacetic acid, optionally substituted triarylmethylamino, formylamino or 2-acetyl-lower alk-1-en-1-ylamino can be cleaved, for example, by treatment with an acid, such as a mineral acid, for example hydrochloric acid, or with an organic acid, for example formic acid or trifluoroacetic acid, optionally in the presence of water, and an amino group protected by an organic silyl group can be cleaved, for example by hydrolysis or alcoholysis. An amino group protected by 2-haloacetyl, for example 2-chloroacetyl, can be cleaved, by treatment with thiourea in the presence of a base, or with a thiolate salt, such as an alkali metal thiolate, of thiourea and by subsequent solvolysis, such as alcoholysis or hydrolysis, of the resulting condensation product. An amino group protected by 2-substituted silylethoxycarbonyl can also be converted into the free amino group by treatment with a salt of hydrofluoric acid yielding fluoride anions, as indicated above in connection with the freeing of a correspondingly protected carboxy group.

Amino protected in the form of an azido group is converted into free amino, for example, by reduction, by treatment with zinc in the presence of an acid, such as acetic acid. The catalytic hydrogenation is preferably carried out in an inert solvent, such as a halogenated hydrocarbon, for example methylene chloride, or alternatively in water or a mixture of water and an organic solvent, such as alcohol or dioxan, at approximately 20°C to 25°C, or alternatively while cooling or heating.

A hydroxy group protected by a suitable acyl group, an organic silyl group or by optionally substituted 1-phenyl-lower alkyl is freed in the same manner as a correspondingly protected amino group. A hydroxy group protected by 2,2-dichloroacetyl is freed, for example, by basic hydrolysis, whilst a hydroxy group etherified by tert.-lower alkyl or by a 2-oxa- or 2-thia-aliphatic or -cycloaliphatic hydrocarbon radical is freed by acidolysis, for example by treatment with a mineral acid or a strong carboxylic acid, for example trifluoroacetic acid.

A protected, especially esterified, sulpho group is freed analogously to a protected carboxy group.

The cleaving reactions described are carried out under conditions known *per se*, if necessary while cooling or heating, and optionally in an inert gas atmosphere, for example a nitrogen atmosphere.

When several protected functional groups are present, the protecting groups are preferably so chosen that more than one such group can be removed simultaneously, for example by acidolysis, such as by treatment with trifluoroacetic acid or formic acid, or by reduction, such as by treatment with zinc and acetic acid.

**Esterification of a free carboxy group**

The conversion of a free carboxy group, for example of a free carboxy group $R_3$, into an esterified carboxy group, especially into a carboxy group that can be cleaved under physiological conditions, may be effected according to esterification methods known *per se*. For example, a compound of the formula I in which the carboxy group to be esterified is in free form and any other functional groups present, for example amino or hydroxy groups, are in protected form, or a compound of the formula I in which the carboxy group to be esterified is in the form of a reactive functional derivative, or a salt of a compound of the formula I is reacted with the corresponding alcohol or with a reactive functional derivative of this alcohol.

In the esterification, with the desired alcohol, of a compound of the formula I in which the carboxy group to be esterified is in free from the same condensation agents, for example carbodiimides, and the same solvents are used and the same reaction conditions are observed as in the acylation according to process a).

A compound of the formula I in which the carboxy group to be esterified is in the form of a reactive functional derivative is, for example, a mixed anhydride or an activated ester, which can be obtained in the manner described under process a) (acylation) by condensation of the carboxylic acid of

the formula I with an inorganic acid, a carboxylic acid, a semi-ester of carbonic acid or with a sulphonic acid or by condensation with a vinylogous alcohol.

A reactive functional derivative of the alcohol to be esterified is especially the ester that is formed by condensation with a strong inorganic or organic acid, for example, the corresponding halide, for example chloride, bromide or iodide, or the corresponding lower alkanesulphonyloxy compound for example the methanesulphonyloxy or 4-methanesulphonyloxy compound.

In the esterification, with the corresponding alcohol, of a compound of the formula I in which the carboxy group to be esterified is in the form of a reactive functional derivative, or in the esterification, with a reactive functional derivative of the corresponding alcohol, of a compound of the formula I in which the carboxy group to be esterified is in free form the same solvents are used and the same reaction conditions are observed as in the acylation with a reactive functional derivative of a carboxylic acid of the formula III in accordance with process a).

A compound of the formula I in which the carboxy group to be esterified is in the form of a reactive functional derivative may also be manufactured *in situ* analogously to the method described under process a) (acylation) and reacted with the corresponding alcohol without being isolated.

**Salt formation**

Salts of compounds of the formula I can be manufactured in a manner known *per se*. Thus, salts of compounds of the formula I can be formed, for example, by reaction of the acidic groups with metal compounds, such as alkali metal salts of suitable carboxylic acids, for example, the sodium salt of α-ethylcaproic acid or sodium carbonate, or with ammonia or a suitable organic amine, preferably stoichiometric quantities or only a small excess of the salt-forming agent being used. Acid addition salts of compounds of the formula I are obtained in the customary manner, for example by treatment with an acid or a suitable anion exchange reagent. Internal salts of compounds of the formula I can be formed, for example by neutralising salts, such as acid addition salts, to the isoelectric point, for example with weak bases, or by treatment with liquid ion exchangers.

Salts can be converted into the free compounds in customary manner; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts can be converted, for example, by treatment with a suitable basic agent.

In all the reactions mentioned hereinbefore that are carried out under basic conditions, all or some of the 3-cephem compounds may be isomerised to 2-cephem compounds. A resulting 2-cephem compound or a mixture of a 2- and a 3-cephem compound can be isomerised in a manner known *per se* to form the desired 3-cephem compound.

Mixtures of isomers can be separated into the individual isomers in a manner known *per se*, for example by fractional crystallisation, chromatography, *etc.*

The process also includes those embodiments according to which compounds formed as intermediates are used as starting materials and the remaining process steps are carried out with these, or the process is discontinued at any stage; furthermore, starting materials may be used in the form of derivatives or may be formed during the reaction.

Preferably, the starting materials and the reaction conditions are so chosen that the compounds described above as being especially preferred are obtained.

**Pharmaceutical preparations**

The pharmacologically acceptable compounds of the formula I, their hydrates or salts, can be used for the manufacture of pharmaceutical preparations.

Pharmaceutical preparations contain an effective amount of the pure active ingredient of the formula I alone or an effective amount of the active ingredient of the formula I in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers, which are preferably suitable for parenteral administration.

Preferably, the active ingredients of the formula I of the present invention are used in the form of injectable, for example intravenously administrable, preparations or in the form of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions which can be prepared before use, for example, from lyophilised preparations that contain only the active ingredient or the active ingredient together with a carrier, for example, mannitol. The pharmaceutical preparations are preferably sterilised and may contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The pharmaceutical preparations in question which, if desired, may contain other pharmacologically valuable substances, for example other active ingredients, contain approximately 0.1% to 100%, especially approximately 1% to 100% of the active ingredient.

The pharmaceutical preparations are produced in a manner known *per se*, for example by means of conventional dissolving or lyophilising processes.

**Use**

Compounds of the formula I, their hydrates or pharmaceutically acceptable salts can be used as antibiotically active agents in the form of pharmaceutical preparations in a method for the therapeutic

treatment of the human or animal body, for example for the treatment of infections that are caused by gram-positive or gram-negative bacteria and cocci, for example by enterobacteria, for example *Escherichia coli, Klebsiella pneumoniae* or *Proteus spp.*

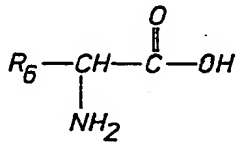
Depending on the nature of the infection and the condition of the infected organism, daily doses of from approximately 0.5 g to approximately 5 g are used s.c., i.v. or i.m. for the treatment of warm-blooded animals (humans and animals) weighing approximately 70 kg.

**Starting materials**

The starting materials used in the process for the manufacture of compounds of the present invention are either known or, if novel, can be manufactured in a manner known *per se*.

Starting materials of the formula II and corresponding compounds having protected functional groups are known or can be manufactured in a manner known *per se*.

Compounds of the formula III in which $R_5$ and $R_6$ have the meanings given under formula I and any functional group present in $R_5$ and/or $R_6$ is present in free or protected form and which have been developed especially for the manufacture of compounds of the formula I are novel and the present invention relates also to these. They are manufactured, for example, as follows: in a compound of the formula



(VII)

in which $R_6$ has the meanings given under formula I and any functional group present in $R_6$ is in protected form, the 2-amino group is acylated with a sulphonic acid of the formula

$$R_5—SO_2—OH \qquad (V)$$

in which $R_5$ has the meaning given under formula I and any functional group present in $R_5$ is in protected form, or with a reactive functional acid derivative or a salt thereof, and, if desired, any protecting groups present in a resulting compound are removed, and/or a resulting compound of the formula III is converted into a different compound of the formula III.

In a compound of the formula VII, any functional group present in $R_6$, for example a carboxy, amino or hydroxy group, is protected by a protecting group mentioned hereinbefore, for example by a carboxy-, amino- or hydroxy-protecting group. The 2-amino group in a compound of the formula VII is optionally protected by a group allowing the sulphonylation reaction. Such a group is described hereinbefore under process b) (sulphonylation) for starting materials of the formula IV.

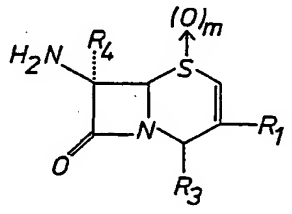
In a compound of the formula V, any functional group present in $R_5$, for example a carboxy, amino or hydroxy group, may be protected by a protecting group mentioned hereinbefore, for example by a carboxy-, amino- or hydroxy-protecting group.

The sulphonylation of a compound of the formula VII with a sulphonic acid of the formula V or with a reactive functional derivative thereof is effected in a manner analogous to that described under process b) (sulphonylation).

In a resulting compound of the formula III having protected functional groups, a protecting group can be removed, optionally selectively, or any functional group which may have been freed in the acylation reaction can be protected.

Compounds of the formulae IV and V, and corresponding compounds having protected functional groups, are known or can be manufactured in a manner known *per se*.

2-cephem compounds of the formula VI are novel. They can be manufactured analogously to acylation process a) or analogously to sulphonylation process b) using as starting material a 2-cephem compound of the formula



(VIII)

which is either known or can be manufactured in a manner known *per se*. Furthermore, 2-cephem compounds of the formula VI can be formed as by-products in processes a) and b), especially if the processes are carried out under basic conditions.

The following Examples serve to illustrate the invention; temperatures are given in degrees Centigrade. The wavelengths of the UV spectra are given in nanometres (nm) and the ε-values are given in brackets. For the IR spectra, the wave numbers ($cm^{-1}$) are given.

The following abbreviations are used in the Examples:

BOC: tert.-butoxycarbonyl

m.p.: melting point

TLC: thin-layer chromatography: on silica gel ready-made plates SL 254 by Antec Birsfelden, Switzerland

$R_f$ 96: $R_f$ value in the solvent system sec.-butanol/glacial acetic acid/water 67:10:23.

**Example 1**

**a) The sodium salt of 3-acetoxymethyl-7β[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

2.6 g of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 1b) are dissolved at room temperature in a mixture of 4 ml of $CH_2Cl_2$ and 0.62 ml of anisole. 10 ml of $CF_3COOH$, cooled to 0°, are then added and the mixture is stirred, without cooling, for 45 minutes. After the addition of 750 ml of hexane/ether (2:1), the mixture is stirred for 5 minutes, the precipitate is filtered off with suction and washed with 100 ml of hexane/ether (1:1) mixture. The filtration residue is then dissolved in 20 ml of methanol, 100 ml of water are added, the mixture is adjusted to pH 7 by the addition of 1N aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic phase is washed three times with water. All the aqueous phases are combined and concentrated *in vacuo* to approximately 10 ml. This solution is chromatographed over 130 g of silylated silica gel (Antec Opti U.P.C.-12) (eluant for fractions 1—25: water, for the subsequent fractions: water/$CH_3CN$ 95:5; fraction size 25 ml). The product-containing fractions are combined, concentrated to a volume of approximately 10 ml and introduced into 400 ml of ethanol. The product which precipitates is filtered off, washed twice with ethanol and twice with diethyl ether and dried. The hydrate of the title compound is obtained; m.p. above 180° (with decomposition); $[\alpha]_D^{20°} = +101° \pm 1°$ (0.93% in $H_2O$); IR: 3600—2400 (broad), 1170, 1748 (shoulder), 1730 (shoulder), 1692, 1610, 1530 (Nujol); UV: 253 (12100; $H_2O$).

**b) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

3.2 g of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 1c) in 30 ml of absolute tetrahydrofuran and 0.37 ml of pyridine are stirred for 3 hours at room temperature with 0.39 ml of methanesulphonyl chloride. The mixture is then concentrated *in vacuo*, taken up in ethyl acetate, washed with 1N hydrochloric acid and NaCl solution, neutralised with 1N $NaHCO_3$ solution, again washed with NaCl solution, dried over $Na_2SO_4$ and concentrated by evaporation *in vacuo*. The resulting crude product is chromatographed over 200 g of silica gel (fraction size: 50 ml; eluant: ether). By combining the product-containing fractions the title compound is obtained; IR: 3400, 1780, 1715 (broad), 1630, 1525 ($CH_2Cl_2$); UV: 257 (13800; $C_2H_5OH$).

**c) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

5.7 g of zinc dust are added in portions in the course of 10 minutes while stirring at 0° to a solution of 5.7 g of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, obtainable according to Example 1d), in 60 ml of an acetic acid/acetonitrile (1:1) mixture and stirring is then continued at 0° for a further 3 hours. The zinc dust residue is then filtered with suction from the reaction solution and the filtrate is washed with acetonitrile and concentrated in a rotary evaporator. Water is added to the residue, the whole is adjusted to pH 8 with 2N NaOH, extracted with ethyl acetate and washed neutral with NaCl solution. The crude product obtained after drying over sodium sulphate and concentration by evaporation is chromatographed over 180 g of silica gel, fractions of 150 ml being taken. Eluant: ethyl acetate and ethyl acetate/methanol (9:1). By combining the product-containing fractions, concentrating them by evaporation and re-precipitating the evaporation residue from $CH_2Cl_2$/hexane, the title compound is obtained; IR: 3370, 1780, 1740—1690 (broad), 1600 ($CH_2Cl_2$); UV: 257 (10500; $C_2H_5OH$).

**d) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

4.3 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-acetic acid obtainable according to Example 1e) and 4.2 g of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester are dissolved in 50 ml of absolute tetrahydrofuran together with 0.8 g of hydroxybenzotriazole. There is then added immediately, after 1 1/2 hours and after 3 hours, in each case 0.71 g of dicyclohexyl carbodiimide in 60 ml of tetrahydrofuran and the mixture is stirred at

room temperature for 6 hours in all. The reaction mixture is poured into 1 litre of hexane/ether (9:1), filtered with suction and washed with hexane. The residue is introduced into 1 litre of ethyl acetate and stirred. The dicyclohexylurea which is insoluble in ethyl acetate is filtered off and the ethyl acetate solution is washed in succession with saturated sodium bicarbonate solution and saturated sodium chloride solution. After drying over $Na_2SO_4$ and concentration by evaporation, the crude product is chromatographed over 200 g of silica gel (fraction size: 150 ml; eluant: hexane/ether 7:3). In so doing, the title compound is obtained; IR: 3390, 1780, 1725 (broad), 1690, 1635, 1528 ($CH_2Cl_2$); UV: 259 (13330: $C_2H_5OH$).

**e) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-acetic acid**

5g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-acetic acid methyl ester obtainable according to Example 1f) are dissolved in 50 ml of methanol. 25 ml of 1N aqueous NaOH are then added and the mixture is stirred at room temperature for 1/2 hour. The mixture is then extracted with ethyl acetate and washed twice with water. The combined aqueous portions are then cooled to 0°, adjusted to pH 3 with 4N hydrochloric acid, extracted with ethyl acetate, washed neutral with saturated aqueous NaCl solution, dried over $Na_2SO_4$ and concentrated by evaporation. This yields the title compound which is further processed without being characterised; IR: 3400, 3300—2750 (broad), 1725 (broad), 1540, 1500 ($CH_2Cl_2$).

**f) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,2,2-trichloroethoxycarbonylamino)-acetic acid methyl ester**

8.61 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine methyl ester are dissolved in a mixture of 85 ml of absolute tetrahydrofuran and 2.66 ml of pyridine. A solution of 4.4 ml of chloroformic acid 2,2,2-trichloroethyl ester in 50 ml of absolute tetrahydrofuran is then added dropwise at 5—10° and the mixture is stirred for one hour in an ice bath. The mixture is then concentrated in a rotary evaporator, taken up in ethyl acetate, washed until neutral with saturated aqueous $NaHCO_3$ solution and saturated NaCl solution, dried over sodium sulphate and concentrated by evaporation. The resulting crude product is chromatographed over silica gel (fractions of 200 ml; eluant:hexane/ether 1:1). After crystallisation of the product-containing fractions, the title compound is obtained; IR: 3407, 1750 (shoulder), 1737, 1726 (shoulder) 1540, 1502 ($CH_2Cl_2$); UV: 258 (8806; $CH_3OH$).

**Example 2**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a) 2.41 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 2b) are reacted in 6 ml of $CH_2Cl_2$ and 2 ml of anisole with 25 ml of trifluoroacetic acid, worked up, chromatographed and re-precipitated. The hydrate of the title compound is obtained; m.p. above 200° (with decomposition); $[\alpha]_D^{20°}=+117°\pm1°$ (1.05% in $H_2O$); IR: 3600—2500, 1760, 1680, 1600, 1520 (Nujol); UV: 250 (10000; $C_2H_5OH$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 1b) 1 g of the *p*-toluenesulphonic acid salt of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 2c) is reacted at 0° in 10 ml of absolute tetrahydrofuran and 0.219 ml of pyridine with 0.119 ml of methanesulphonyl chloride and worked up. The resulting crude product is chromatographed over 50 g of silica gel (eluant:toluene/ethyl acetate (9:1) and 85:15); fraction size: 50 ml). The product-containing fractions are combined and concentrated by evaporation. The evaporation residue is reprecipitated from methylene chloride/hexane. The title compound is obtained; $[\alpha]_D^{20°}=+11°\pm1°$ (1.07% in $CHCl_3$); IR: 3400, 3290, 1780, 1715, 1690 (shoulder), 1630, 1530 ($CH_2Cl_2$); UV: 259 (14300; $C_2H_5OH$).

The starting material is prepared as follows:

**c) The *p*-toluenesulphonic acid salt of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

7.21 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-BOC-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 2d) are stirred at room temperature for 8 hours with 3.8 g of *p*-toluenesulphonic acid monohydrate in 100 ml of acetonitrile. After precipitation with 1000 ml of ether, filtration of the precipitate with suction, washing with 500 ml of ether and drying *in vacuo*, the title compound is obtained which is further processed without being characterised.

**d) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-BOC-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

2.21 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-BOC-aminoacetic acid obtainable according to Example 2e) are dissolved in 50 ml of absolute tetrahydrofuran, the solution is cooled to —20° and 0.756 ml of N-methylmorpholine and 0.728 ml of chloroformic acid isobutyl ester are added in succession. The mixture is then stirred for 3 hours at —20°, the temperature is reduced to —40°, 2.0 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in solid form are added, the mixture is stirred for 10 minutes at —40° and for 2 1/2 hours at 0° and then worked up as follows:

The reaction mixture is taken up in ethyl acetate and washed in succession with 1N aqueous hydrochloric acid, saturated aqueous $NaHCO_3$ solution and NaCl solution until neutral. The organic phase is dried over sodium sulphate, concentrated by evaporation *in vacuo* and the crude product is chromatographed over 100 g of silica gel (eluant:toluene/ethyl acetate (95:5) and (4:1); fraction size: 100 ml). The product-containing fractions are combined concentrated by evaporation and the evaporation residue is re-precipitated from methylene chloride/ether. The title compound is obtained; $[\alpha]_D^{20}=+11°\pm1°$ (0.86% in $CHCl_2$); IR: 3390, 1778, 1715, 1692, 1635, 1528 ($CH_2Cl_2$); UV: 258 (14500; $C_2H_5OH$).

**e) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-BOC-aminoacetic acid**

15 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine methyl ester are stirred at room temperature for one hour in a mixture of 52.5 ml of methanol and 34.5 ml of water with 105 ml of 1N aqueous sodium hydroxide solution. The mixture is then extracted with ethyl acetate and washed twice with 50 ml of water each time. 100 ml of dioxan and 14 g of di-tert.-butyl pyrocarbonate are added to the combined aqueous phases and the mixture is then stirred at room temperature for 3 hours, the pH being maintained constant at 8 by the addition of 1N aqueous sodium hydroxide solution (titrator). The mixture is then extracted with ethyl acetate and washed three times with water. The combined aqueous portions are adjusted at 0° to pH 2 with 4N hydrochloric acid and extracted with ethyl acetate. The ethyl acetate phase is washed neutral with sodium chloride solution, dried over sodium sulphate and concentrated by evaporation *in vacuo*. The resulting crude product is recrystallised from a mixture of methanol/methylene chloride/ether/hexane. In so doing, the title compound is obtained; m.p 168°; IR: 3410, 3300—2800 (broad), 1760 (shoulder), 1725, 1540, 1500 ($CH_2Cl_2$).

**Example 3**

**a) 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(4-aminobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 0.4 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(4-aminobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 3b) are reacted in 0.98 ml of $CH_2Cl_2$ and 0.3 ml of anisole with 3.7 ml of trifluoroacetic acid, worked up, chromatographed and re-precipitated. The hydrate of the title compound is obtained; m.p. above 205° (with decomposition); $[\alpha]_D^{20°}=+102°\pm1°$ (0.78% in $H_2O$); IR: 3600—2500 (broad), 1760, 1680, 1620 (shoulder), 1595, 1520 (Nujol); UV: 259 (21000; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(4-aminobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 1c), 0.95 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(4-(2,2,2-trichloroethoxycarbonylamino)-benzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 3c) are reacted in 10 ml of acetonitrile/acetic acid (1:1) mixture with 0.87 g of zinc dust, worked up and chromatographed. In so doing, the title compound is obtained; $[\alpha]_D^{20°}=+15°+1°$ (0.77% in $CHCl_3$); IR: 3390, 3280, 1770, 1835, 1690, 1620, 1590, 1530 ($CH_2Cl_2$); UV: 262 (29800; $C_2H_5OH$).

**c) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(4-(2,2,2-trichloroethoxycarbonylamino)-benzenesulphonylamino)-acetamido]-3- cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 1b), 3.27 g of the *p*-toluenesulphonic acid salt of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 4a) are reacted at room temperature in 30 ml of absolute tetrahydrofuran and 0.72 ml of pyridine with 2.58 g of 4-(2,2,2-trichloroethoxycarbonylamino)-benzenesulphonyl chloride and worked up. The resulting crude product is chromatographed over 100 g of silica gel (eluant: toluene/ethyl acetate (9:1) and 85:15); fraction size; 100 ml). The product-containing fractions are combined, concentrated by evaporation and reprecipitated from methylene chloride/hexane. The title compound is obtained: $[\alpha]_D^{20°}=+7°\pm1°$ (0.94% in $CHCl_3$); IR: 3400, 3280, 1770, 1750, 1735, 1590, 1530 ($CH_2Cl_2$); UV: 254 (36400; $C_2H_5OH$).

**d) 4-(2,2,2-trichloroethoxycarbonylamino)-benzenesulphonyl chloride**

17.3 g of sulphanilic acid are made into a slurry at 0° in 100 ml of pyridine. 15.1 ml of chloroformic acid 2,2,2-trichloroethyl ester are then added dropwise at 0° in the course of one hour

while stirring vigorously and the mixture is then stirred for 16 hours at room temperature. The mixture is then concentrated to dryness by evaporation *in vacuo*, taken up repeatedly in toluene and concentrated by evaporation again each time. Finally, the evaporation residue is dried for 60 hours *in vacuo* at 50°. The mixture is then made into a slurry in 250 ml of absolute chloroform and the slurry is heated to 40°. Thereupon a total of 33.75 g of solid phosphorus pentachloride are added in portions in the course of one hour while stirring at 40° and the mixture is then heated under reflux for 4 hours. The cooled reaction mixture is taken up in 2.7 litres of toluene, washed four times with ice-water, dried over sodium sulphate and concentrated by evaporation. After crystallisation of the crude product from $CH_2Cl_2$/hexane, the title compound is obtained. M.p. 90—91°; IR: 1757, 1591, 1525, 1407, 1375 ($CH_2Cl_2$).

**Example 4**

**a) The *p*-toluenesulphonic acid salt of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

2 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-benzyloxycarbonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are hydrogenated in 50 ml of absolute glacial acetic acid in the presence of 2 g of 10% palladium-on-carbon catalyst. After the absorption of 1 equivalent of hydrogen (the $CO_2$ liberated during hydrogenation is absorbed in aqueous KOH) the reaction is terminated, the catalyst is filtered off and the filtrate is concentrated to dryness by evaporation *in vacuo*. The evaporation residue is taken up in ethyl acetate and washed in succession with 1N aqueous $NaHCO_3$ solution and NaCl solution until neutral. The mixture is then dried over sodium sulphate and concentrated by evaporation. The crude amine is dissolved in 20 ml of acetonitrile, 1.0 g of *p*-toluenesulphonic acid monohydrate is added and the mixture is stirred at room temperature for 10 minutes. After precipitation with 500 ml of ether, filtration of the precipitate with suction, washing with 250 ml of ether and drying *in vacuo*, the title compound is obtained which is identical to the toluene-sulphonic acid salt described in Example 2c).

The starting material is prepared as follows:

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-benzyloxycarbonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 2d), 4.4 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-benzyloxy-carbonylaminoacetic acid obtainable according to Example 4c) and 3.63 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted (1.38 ml of N-methylmorpholine 1.33 ml of chloroformic acid isobutyl ester, 142 ml of tetrahydrofuran), worked up, chromatographed (eluant: toluene/ethyl acetate (9:1 and 4:1); fraction size: 300 ml) and re-precipitated. The title compound is obtained; $[\alpha]_D^{20°}=+12°\pm1°$ (1.04% in $CHCl_3$); IR: 3400, 1790, 1727, 1698, 1638, 1543, 1498 ($CH_2Cl_2$); UV: 258 (15000; $C_2H_5OH$).

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-benzyloxycarbonylaminoacetic acid**

7.4 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-benzyloxycarbonylaminoacetic acid methyl ester obtainable according to Example 4d) are dissolved in 270 ml of methanol. 60 ml of 1N aqueous sodium hydroxide solution are then added and the mixture is stirred at room temperature for 3 hours. After working up analogously to Example 1e), the title compound is obtained; IR: 3410, 3300—2800 (broad), 1760 (shoulder), 1725, 1542, 1503 ($CH_2Cl_2$); UV: 259 (8400; $C_2H_5OH$).

**d) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-benzyloxycarbonylaminoacetic acid methyl ester**

8.61 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine methyl ester are dissolved in a mixture of 85 ml of absolute tetrahydrofuran and 2.66 ml of pyridine. A solution of 4.74 ml of benzyloxycarbonyl chloride in 50 ml of absolute dioxane is then added dropwise in the course of 15 minutes while stirring at 0° and stirring is continued at 0° for 3 hours. The mixture is then taken up in ethyl acetate, washed with 1N aqueous HCl, with 1N aqueous $NaHCO_3$ and with saturated aqueous NaCl solution until neutral, dried over sodium sulphate and concentrated by evaporation. The resulting crude product is chromatographed over 400 g of silica gel (fractions of 500 ml; eluant:toluene/ethyl acetate 95:5). After combining the product-containing fractions, the title compound is obtained; IR: 3410, 1748 (shoulder), 1540, 1502; UV: 258 (8800; $C_2H_5OH$).

**Example 5**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.367 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-ethane-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenyl methyl ester obtainable according to Example 5b) is reacted in 3.6 ml of $CH_2Cl_2$ and 1.12 ml of anisole with 13.9 ml of trifluoroacetic acid, worked up, chromatographed and re-precipitated. The hydrate of the title compound is obtained; m.p. above 205° (with decomposition); $[\alpha]_D^{20°}=+116°\pm1°$ (0.73% in $H_2O$); IR: 3600, 2500 (broad), 1760, 1680, 1640 (shoulder), 1600, 1520 (Nujol); UV: 251 (9800; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 1b), 3.5 g of the *p*-toluenesulphonic acid salt of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 40 ml of absolute tetrahydrofuran in the presence of 1 ml of pyridine with 0.8 ml of ethanesulphonyl chloride, worked up, chromatographed and re-precipitated. The title compound is obtained; $[\alpha]_D^{20°}=+18°\pm1°$ (0.97% in $CHCl_3$); IR: 3380, 3280, 1775, 1710, 1690 (shoulder), 1630, 1525 ($CH_2Cl_2$); UV: 258 (14300; $C_2H_5OH$).

**Example 6**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminocarbonylamino-1,3,4-thiadiazol-5-ylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a) 4.5 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylaminocarbonylamino-1,3,4-thiadiazol-5-ylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 6b) are reacted in 9 ml of $CH_2Cl_2$ and 1.27 ml of anisole with 20 ml of trifluoroacetic acid, worked up, chromatographed and re-precipitated. The hydrate of the title compound is obtained; m.p. above 220° (with decomposition); $[\alpha]_D^{20°}=+71°\pm1°$ (0.93% in $H_2O$); IR: 3600—2500 (broad), 1766, 1690, 1605, 1520 (Nujol); UV: 262 (14800; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylaminocarbonylamino-1,3,4-thiadiazol-5-yl-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

4.5 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylaminocarbonylamino-1,3,4-thiadiazol-5-ylsulphonylamino)-acetic acid obtainable according to Example 6c) and 3.3 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester are dissolved in 50 ml of absolute tetrahydrofuran together with 0.8 g of hydroxybenzotriazole. There is then added immediately, after 1 1/2 hours and after 3 hours, in each case 0.71 g of dicyclohexyl carbodiimide in 60 ml of tetrahydrofuran and the mixture is stirred at room temperature for 6 hours in all. The reaction mixture is poured into 1 litre of hexane/ether (9:1) mixture, filtered with suction and washed with hexane. The residue is introduced into 1 litre of ethyl acetate and stirred. The dicyclohexylurea which is insoluble in ethyl acetate is filtered off and the ethyl acetate solution is washed in succession with saturated sodium bicarbonate solution and saturated sodium chloride solution. The crude product obtained after drying and concentration by evaporation of the ethyl acetate phase is chromatographed over 200 g of silica gel (eluant: ether/ethyl acetate (1:1) and ethyl acetate; fraction size: 100 ml). After combining and re-precipitating the product-containing fractions from $CH_2Cl_2$/hexane, the title compound is obtained; $[\alpha]_D^{20°}=+25°\pm1°$ (1.01% in $CHCl_3$); IR: 3400—2806, 1778, 1700, 1530 ($CH_2Cl_2$); UV: 263 (21600; $C_2H_5OH$).

The starting material is prepared as follows:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylaminocarbonylamino-1,3,4-thiadiazol-5-ylsulphonylamino)-acetic acid**

2.73 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine are heated, using a reflux condenser, with 8 ml of N,O-bis (trimethylsilyl)acetamide in 24 ml of $CH_2Cl_2$ for 1 1/2 hours, with a clear solution being formed. The solution is then cooled to 0°, and 0.81 ml of pyridine and 3.8 g of 2-methylamino-carbonylamino-1,3,4-thiadiazol-5-ylsulphonyl chloride are added in succession and the mixture is then stirred for one hour at 0° and for 16 hours at room temperature. The mixture is then taken up in ethyl acetate, washed twice with 1N hydrochloric acid and four times with saturated aqueous NaCl solution, dried over sodium sulphate and concentrated to dryness by evaporation *in vacuo*. The resulting title compound is further processed without being characterised (Example 6b)).

**Example 7**

**a) The sodium salt of 7β-[(2R)-2-(aminothiazol-4-yl)-2-methanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.21 g of the 7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-methane-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 7b) are reacted in 3 ml of $CH_2Cl_2$ and 1 ml of anisole with 12 ml of trifluoroacetic acid, worked up, chromatographed and re-precipitated. The hydrate of the title compound is obtained; m.p. above 206° (with decomposition); IR: 3600—2500, 1766, 1680, 1600, 1520 (Nujol); UV: 250 (10500; $H_2O$).

**b) 7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 1b), 4.36 g of the 7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 7c) are reacted with 0.81 ml of methanesulphonyl chloride in 50 ml of absolute tetrahydrofuran and

0.56 ml of pyridine (duration of reaction 16 hours) and worked up. The resulting crude product is chromatographed analogously to Example 2b). In so doing, the title compound is obtained; $[\alpha]_D^{20°}$=—4°±1° (0.94% in $CHCl_3$); IR: 3400, 3290, 1780, 1715, 1690 (shoulder), 1630, 1530 ($CH_2Cl_2$); UV: 259.

The starting material can be prepared as follows:

**c) 7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

4 g of the 7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-chloroacetylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 7d) are stirred with 0.94 g of thiourea in a mixture of 70 ml of dioxan and 1.37 ml of acetic acid at room temperature for 5 hours and then at 50° for 10 hours. The reaction mixture is then diluted with ethyl acetate, washed once with saturated aqueous $NaHCO_3$ solution and also with saturated aqueous NaCl solution until neutral. The crude title compound obtained after drying over $Na_2SO_4$ and concentration by evaporation is further processed directly (Example 7b)).

**d) 7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-chloroacetylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-chloroacetyl-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 9.6 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-chloroacetylamino-acetic acid are reacted with 9.1 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 80 ml of tetrahydrofuran (2.4 g of hydroxybenzotriazole; three times 2.2 g of dicylohexylcarbodiimide each time in 20 ml of tetrahydrofuran) and worked up. The resulting crude product is chromatographed in 4 equal portions over 500 g of silical gel in each case (eluant:toluene/ethyl acetate 85:15 mixture; fractions of 25 ml). In so doing, the (2R)-title compound is diluted first: $[\alpha]_D^{20°}$=—5°±1° (0.81% in $CHCl_3$); IR: 3380, 3250, 1780, 1715, 1700 (shoulder), 1670, 1510 (broad) ($CH_2Cl_2$); UV: 258 (13500; $C_2H_5OH$).

The configuration at the C-2 carbon atom of the acetic acid in the acyl side chain for the (2R)- and the (2S)-compound is assigned on the basis of rotational shifts and NMR-comparisons (CH-7) with ureidocephalosporins; *cf.*, for example, Breuer *et al.*, J. Antibiot. 31, 546—560 and German Offenlegungsschrift 2 924 296.

The fractions next eluted consist of a binary mixture of the above compound and the corresponding (2S)-isomer, which can be further separated by repeating the chromatography. Finally, pure (2S)-title compound is eluted; $[\alpha]_D^{20°}$=+42°±1° (0.82% in $CHCl_3$); IR: 3390, 3270, 1780, 1715, 1700 (shoulder), 1670 (shoulder), 1520 (broad) ($CH_2Cl_2$); UV: 259 (14200; $C_2H_5OH$).

**e) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-chloroacetylaminoacetic acid**

10 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine methyl ester are dissolved in 35 ml of methanol, and 23 ml of $H_2O$ and 70 ml of 1N aqueous sodium hydroxide solution are added in succession. The mixture is then stirred at room temperature for one hour. The mixture is then cooled to 0° and 2.9 ml of chloroacetyl chloride are added dropwise in the course of 5 minutes, during which the pH should be maintained constant at 10 by the addition of 2N sodium hydroxide solution (titrator). Then, at pH 10 and 0° (2N NaOH; titrator), the mixture is stirred for a further 2 hours. For working up, the mixture is adjusted to pH 2 with 4N hydrochloric acid, extracted with ethyl acetate and washed 6 times with saturated aqueous NaCl solution. The crude product obtained after drying over sodium sulphate and concentration by evaporation is re-precipitated, from a mixture of $CH_3OH/CH_2Cl_2$/hexane. In so doing, the title compound is obtained which is further processed directly (Example 7d)).

**Example 8**

**a) The sodium salt of 7β-[(2S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.4 g of the 7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-methane-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 8b) are reacted in 6 ml of $CH_2Cl_2$ and 2 ml of anisole with 25 ml of trifluoroacetic acid, worked up, chromatographed and re-precipitated. The hydrate of the title compound is obtained; m.p. above 200° (with decomposition); $[\alpha]_D^{20°}$=+126°±1° (0.94% in $H_2O$); IR: 2600—2500, 1760, 1680, 1600, 1520 (Nujol); UV: 250 (9900; $H_2O$).

**b) 7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 7b), 4.48 g of the 7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-amino-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 8c) are reacted with 0.83 ml of methanesulphonic acid chloride in 5 ml of tetrahydrofuran and 0.58 ml of pyridine, worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}$=+36°±1° (0.89% in

$CHCl_3$); IR: 3400, 3290, 1780, 1715, 1690 (shoulder), 1630 1530 ($CH_2Cl_2$); UV: 259 (14400; $C_2H_5OH$).

The starting material is prepared as follows:

**c) 7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogouly to Example 7d), 3.89 g of the 7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-chloroacetyl-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 7d) are reacted with 0.91 g of thiourea (70 ml of dioxan and 1.34 ml of acetic acid) and worked up. In so doing, the crude title compound is obtained which is further processed directly (Example 8b)).

**Example 9**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylamino-1,3,4-thiadiazol-5-ylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylamino-1,3,4-thiadiazol-5-ylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 9b) are reacted in 5 ml of $CH_2Cl_2$ and 0.57 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 220° (with decomposition); $[\alpha]_D^{20°}=+89°\pm1°$ (0.92% in $H_2O$); IR: 3600—2500 (broad), 1760, 1690, 1600, 1520 (Nujol); UV: 263 (14800; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylamino-1,3,4-thiadiazol-5-ylsulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylamino-1,3,4-thiadiazol-5-ylsulphonylamino)-acetic acid and 1.83 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 40 ml of tetrahydrofuran (0.8 g of hydroxybenzotriazole, 3×0.47 g of dicyclohexyl carbodiimide each time in 40 ml of tetrahydrofuran), worked up, chromatographed and re-precipitated. The title compound is obtained; $[\alpha]_D^{20°}=+28°\pm1°$ (0.82% in $CHCl_3$); IR: 3400—2700 (broad), 1778, 1720—1690 (broad), 1525 ($CH_2Cl_2$); UV: 263 (20900; $C_2H_5OH$).

**Example 10**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-((1R,S)-1-cyanoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.18 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-((1R,S)-1-cyanoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 10b) are reacted in 8 ml of $CH_2Cl_2$ and 2.5 ml of anisole with 30 ml of trifluoroacetic acid, worked up, chromatographed and re-precipitated. The hydrate of the title compound is obtained; m.p. above 180° (with decomposition); $[\alpha]_D^{20°}=+102°\pm1°$ (0.91% in $H_2O$); IR: 3600—2400 (broad, 2255, 1760, 1680, 1640 (shoulder, 1605, 1520 (Nujol); UV: 250 (10000; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-((1R,S)-1-cyanoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3.92 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-((1R,S)-1-cyanoethanesulphonylamino)-acetic acid obtainable according to Example 10c) and 3.3 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 30 ml of tetrahydrofuran (0.915 g of hydroxybenzotriazole; 3×0.8 g of dicyclohexyl carbodiimide each time in 7 ml of tetrahydrofuran) and worked up. After chromatography of the crude product (eluant:toluene/ethyl acetate 9:1, fraction size: 250 ml), combination of the product-containing fractions and re-precipitation from $CH_2Cl_2$/hexane, the title compound is obtained; $[\alpha]_D^{20°}=+8°\pm1°$ (1.02% in $CHCl_3$); IR: 3400, 3300, 2250 (weak), 1780, 1720, 1700 (shoulder), 1635, 1530 ($CH_2Cl_2$); UV: 258 (14200; $C_2H_5OH$).

The starting material is prepared as follows:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-((1R,S)-2-cyanoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 2.73 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine are reacted in 24 ml of $CH_2Cl_2$with 2.3 g of 1-cyanoethanesulphonyl chloride (8 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained which is further processed without being characterised.

**Example 11**

**a) 3-acetoxymethyl-7β-[(2R,S)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonyl-aminoacetamido]-3-cephem-4-carboxylate**

A solution of 1.6 g of the 3-acetoxymethyl-7β-[(2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid obtainable according to Example 11b) in 3 ml of methylene chloride and 20 ml of trifluoroacetic acid is stirred at room temperature for 30 minutes and then concentrated *in vacuo*. The residue is triturated with diethyl ether. The product is

dissolved in 20 ml of methanol and adjusted to pH 7.0 with a 50% solution of sodium 2-ethyl hexanoate in methanol, and ethyl acetate is added. The product which precipitates is filtered off and chromatographed. The title compound is obtained of $R_f$: approximately 0.60 (silica gel Opti UPC 12, water/methanol 95:5); IR (Nujol): 3310, 1765, 1610, 1155.

**b) 3-acetoxymethyl-7β-[2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

2.3 g (6.5 mmol) of the (2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonyl-aminoacetic acid obtainable according to Example 11c) and 0.77 ml of N-methylmorpholine are introduced at −5° into a stirred suspension of a Vilsmeyer reagent, prepared from 0.63 ml of oxalyl chloride and 0.56 ml of N,N-dimethylformamide in 25 ml of methylene chloride. The mixture is stirred at 0° for 30 minutes and then cooled to −10°. To this mixture there is added dropwise a freshly prepared solution of 1.69 g (6.2 mmol) of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid in 20 ml of methylene chloride and 6.8 ml of N,O-bis(trimethylsilyl)acetamide and the mixture is stirred at 0° under nitrogen for 2 hours. The reaction solution is concentrated, diluted with ethyl acetate and extracted with dilute aqueous sodium bicarbonate solution. The aqueous extracts are adjusted to pH 2.0 with 2N HCl and extracted with ethyl acetate. The organic phase is separated, washed with dilute aqueous sodium chloride solution, dried over magnesium sulphate and concentrated *in vacuo*. The title compound is obtained of $R_f$ 96: approximately 0.45 (silica gel); IR (Nujol): 1765, 1160.

The starting material is prepared as follows:

**c) (2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetic acid**

4.4 g of potassium hydroxide and 36.5 ml of water are added to a solution of 5.0 g (13.6 mmol) of the (2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetic acid methyl ester obtainable according to Example 11d) in 90 ml of 95% ethanol and the mixture is stirred at room temperature for 1.5 hours. The reaction mixture is concentrated *in vacuo*, the residue is dissolved in water, the solution is adjusted to pH 8.5 with dilute hydrochloric acid and extracted with ethyl acetate. The aqueous phase is separated, adjusted to pH 2.0 with 2N HCl and extracted with ethyl acetate. The organic phase is separated, washed with aqueous sodium chloride solution, dried over magnesium sulphate and concentrated. The title compound is obtained of $R_f$ 96: approximately 0.50 (silica gel); UV: 217 (5300), 245 (7700, ethanol).

**d) (2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetic acid methyl ester**

6 ml of triethylamine and a solution of 2.8 ml of mesyl chloride in 15 ml of a methylene chloride are added at −5° to a solution of 8.6 g (29.6 mmol) of the (2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-aminoacetic acid methyl ester obtainable according to Example 11e) in 30 ml of methylene chloride and the mixture is stirred at 0° for 1.5 hours. The reaction mixture is concentrated *in vacuo*, the residue is taken up in ethyl acetate and washed in succession with dilute aqueous sodium bicarbonate solution, water, 1N hydrochloric acid and aqueous sodium chloride solution, dried over magnesium sulphate and concentrated. After chromatographing the residue over silica gel with toluene and an increasing proportion of ethyl acetate, the title compound is obtained of $R_f$: 0.35 (silica gel, toluene/ethyl acetate 1:1); NMR (60 MHz, $CDCl_3$): 1.56, 2.96, 3.70, 5.65 ppm.

**e) (2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-aminoacetic acid methyl ester**

A suspension of 25.0 g (82.5 mmol) of 2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetic acid methyl ester and 25 g of 10% palladium-on-carbon catalyst in 250 ml of methanol is hydrogenated at room temperature for 24 hours. The reaction mixture is filtered over Hyflo-Supercel® and the filtrate is concentrated *in vacuo*. The title compound is obtained having an $R_f$ value of 0.15 (silica gel, chloroform/methanol 95:5); NMR (60 MHz, $CDCl_3$): 1.56, 3.80, 7.07.

**Example 12**

**a) The sodium salt of 7β-[(2R,S)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 11a), 23 ml of trifluoroacetic acid are added to a solution of 2.3 g (3.30 mmol) of the 7β-[(2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 12b) in 5 ml of methylene chloride and 1.7 ml of anisole and the mixture is stirred and concentrated. The residue is triturated with diethyl ether. The product is dissolved in 15 ml of methanol and adjusted to pH 7.0 with a 50% solution of sodium 2-ethyl hexanoate in methanol, and ethyl acetate is added. The product which precipitates is filtered off and chromatographed (silica gel Opti-UPC 12). The title compound is obtained having an $R_f$ value of 0.70 (silica gel Opti-UPC 12, water/methanol 95:5); IR (Nujol): 3310, 1765, 1600, 1155.

**b) 7β-[(2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

0.55 g of 1-hydroxybenzotriazole and 1.25 g of N,N'-dicyclohexyl carbodiimide in 15 ml of dry tetrahydrofuran are added at 0° to a solution of 1.80 g (5.0 mmol) of 2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetic acid and 1.83 g (5 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 25 ml of dry tetrahydrofuran, the mixture is stirred at 0° for 3.5 hours and then heated to room temperature. After filtering the reaction mixture, the filtrate is diluted with ethyl acetate and washed in succession with aqueous dilute sodium bicarbonate, hydrochloric acid and sodium chloride solutions, dried over magnesium sulphate and concentrated *in vacuo*. After triturating the residue with ether, the title compound is obtained; $R_f$: 0.65 (silica gel, ethyl acetate).

**Example 13**

**a) 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

11 ml of cold trifluoroacetic acid are added to a solution, cooled to 0°, of 2.2 g (2.4 mmol) of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 13b) and 2.2 ml of anisole in 11 ml of absolute methylene chloride, the mixture is stirred at 25° under a nitrogen atmosphere for 90 minutes and then, at 0°, 100 ml of diethyl ether are added. The beige precipitate is filtered off, washed with a little diethyl ether and, after being dissolved in 10 ml of water, extracted with ethyl acetate (4×5 ml). The acidic aqueous phase (pH approximately 1.8), cooled to 0°, is adjusted to pH 5 by the dropwise addition of 2N sodium hydroxide solution, and 40 ml of ethanol are added. The precipitate which forms is filtered off, washed with ethanol/water (3:1) and, in order to remove the organic solvent completely, made into a slurry in approximately 10 ml of water and concentrated in a rotary evaporator. After drying (16 hours at 25°, 0.05 torr), the title compound is obtained in the form of the monohydrate; m.p. above 210° (with decomposition); TLC (silica gel, development with ninhydrin): $R_f$ 96: approximately 0.15; $[\alpha]_D^{20°}=+58°\pm1°$ (0.959% in 0.1N HCl); UV: 250 (15000; 0.1N HCl).

**b) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 12b), a solution of 6.81 g (33 mmol) of dicylohexyl carbodiimide in 60 ml of absolute tetrahydrofuran is added in the course of approximately 15 minutes to a solution, cooled to 0°, of 14.4 g (30 mmol) of the (2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid obtainable according to Example 13c) and 4.05 g (30 mmol) of 1-hydroxybenzotriazole in 240 ml of absolute tetrahydrofuran and, thereafter, 11.83 g (27 mmol) of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester are added. After a reaction period of 4 hours at room temperature, the N,N'-dicyclohexylurea which precipitates is filtered off and the filtrate is concentrated in a rotary evaporator. The mixture is worked up analogously to Example 12b) and the title compound is obtained; $R_f$: approximately 0.50 (silica gel, iodine, methylene chloride/ethyl acetate 1:1).

The starting material is prepared as follows:

**c) (2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid**

17.1 g of di-tert.-butyl dicarbonate are added all at once at room temperature to a well stirred suspension of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid and 11.3 g of anhydrous sodium carbonate in 160 ml of dioxan and 80 ml of water. After 2 hours, the reaction mixture, cooled to 0°, is acidified to pH~2 with 4N hydrochloric acid and extracted with ethyl acetate (2×300 ml). The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated. The residue, which is still oily, is triturated with petroleum ether from which, after filtration and drying, the title compound can be isolated as a slightly beige powder; m.p. above 83° (with decomposition); $R_f$ 96: approximately 0.65 (silica gel, UV 366).

**d) (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid**

25 g of zinc dust are added in portions in the course of 15 minutes while stirring vigorously at 0° to a solution of 25.0 g (45 mmol) of (2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 250 ml of acetic acid/acetonitrile 1:1. After a reaction period of one hour at room temperature, another 12.5 g of zinc dust are added. After a further 3 hours, the zinc dust is filtered off from the reaction mixture and the filtrate is concentrated in a rotary evaporator. To remove the excess acetic acid, the residue is, in addition, twice made into a slurry in approximately 50 ml of toluene, concentrated to dryness and then triturated with 250 ml of diethyl ether. The title compound so obtained is used in the next synthesis step (Example 13c) without further purification; $R_f$ 96: approximately 3.38 (silica gel, UV 366).

**e) (2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid**

80.3 ml (0.33 mol) of N,O-bis(trimethylsilyl)acetamide and, after 30 minutes, another 10 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 27.3 g (0.1 mol) of (2R,S)-2-amino-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 273 ml of absolute methylene chloride. After a reaction period of 2½ hours in all at 25°, the clear reaction mixture is cooled to 0° and 8.1 ml of absolute pyridine and 31.9 g (0.1 mol) of 2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonyl chloride, dissolved in 150 ml of absolute methylene chloride, are added. After a reaction period of 2.5 hours at room temperature, the solvent is distilled off and the residue, dissolved in 1 litre of ethyl acetate, is washed with 2x250 ml of 1N hydrochloric acid and 2x200 ml of saturated sodium chloride solution. After drying the organic phase with sodium sulphate and removing the solvent in a rotary evaporator, the title compound is obtained in the form of a pale yellow powder; $R_f$ 96: approximately 0.80 (silica gel, UV: 366).

**Example 14**

**a) 7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a) or 13a), the title compound is obtained in the form of the dihydrate by reacting 2.6 g (3.14 mmol) of the 7β-[(2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 14b) with 13 ml of trifluoroacetic acid and 2.6 ml of anisole in 13 ml of absolute methylene chloride. M.p. above 220° (with decomposition); $R_f$ 96: approximately 0.10 (silica gel, ninhydrin); $R_f$: approximately 0.40 and 0.50 (silica gel Opti-UPC 12, UV 366, water/acetonitrile 9:1); $[\alpha]_D^{20°}=99°\pm1°$ (0.524% in 0.1N HCl); UV: 250 (12900; 0.1N HCl).

**b) 7β[(2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 1b) or 13b), the title compound is obtained by treating 2.4 g (5 mmol) of (2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 1.64 g (4.5 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.68 g of 1-hydroxybenzotriazole and 1.13 g (5.5 mmol) of N,N'-dicyclohexyl carbodiimide in 50 ml of tetrahydrofuran; $R_f$: approximately 0.60 (silica gel, UV 366, methylene chloride/ethyl acetate 1:1).

**Example 15**

**a) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a) or 13a), the title compound is obtained in the form of the dihydrate by treating 5.74 g (6 mmol) of the 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 15b) with 30 ml of trifluoroacetic acid and 5.7 ml of anisole in 30 ml of absolute methylene chloride; m.p. above 192° (with decomposition); $R_f$ 96: approximately 0.13 (silica gel, ninhydrin); $[\alpha]_D^{20°}=+45°\pm1°$ (0.285% in 0.1N hydrochloric acid); UV: 252 (14000 in 0.1N HCl).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 1b) or 13b), the title compound is obtained by treating 4.8 g (10 mmol) of (2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 4.33 g (9 mmol) of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.35 g (10 mmol) of 1-hydroxybenzotriazole and 2.27 g (11 mmol) of N,N'-dicylohexyl carbodiimide in 80 ml of tetrahydrofuran as solvent; $R_f$: approximately 0.44 and 0.54 (silica gel, UV 366, ether/ethyl acetate 1:1). The mixture of 2R- and 2S-diastereoisomers can be separated into the 2R- and 2S-components by chromatography over silica gel.

**Example 16**

**a) 3-methoxy-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a) or 13a), the title compound is obtained in the form of the monohydrate by treating 6.15 g (8.3 mmol) of the 3-methoxy-7β-[(2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 16b) with 32 ml of trifluoroacetic acid and 6.2 ml of anisole in 32 ml of absolute methylene chloride; m.p. above 192° (with decomposition); $R_f$ 96: approximately 0.13 (silica gel, ninhydrin); $[\alpha]_D^{20°}=+110°\pm1°$ (0.33% in 0.1N HCl); UV: 250 (13300 in 0.1N HCl).

**b) 3-methoxy-7β-[(2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 1b) or 13b), the title compound is obtained by treating 4.8 g (10 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 3.94 g (9 mmol) of 3-methoxy-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.35 g of 1-hydroxybenzotriazole and 2.27 g (11 mmol) of N,N'-dicyclohexyl carbodiimide in 80 ml of tetrahydrofuran as solvent; $R_f$: approximately 0.45 (silica gel, UV 366, methylene chloride/ethyl acetate 1:1).

**Example 17**

**a) 3-methoxy-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

1.26 g of zinc dust and, after one hour, another 0.63 g of zinc duct are added while stirring vigorously at room temperature to a solution of 1.01 g (1.2 mmol) of the 3-methoxy-7β-[(2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-thiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid obtainable according to Example 17b) in 15 ml of acetic acid/acetonitrile 1:1. After a further 2 hours, the mixture is concentrated in a rotary evaporator. The residue, dissolved in 10 ml of water, extracted with ethyl acetate (2×5 ml) and the aqueous phase is adjusted to pH 5 with 1N sodium hydroxide solution. The precipitate which forms is filtered off and dried. The title compound so obtained is identical to the product obtained according to Example 16a).

**b) 3-methoxy-7β-[(2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-thiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

7 ml of trifluoroacetic acid are added to a solution of 1.41 g (1.4 mmol) of the 3-methoxy-7β-[(2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-thiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 17c) in 7 ml of methylene chloride and, after 2 hours, the mixture is concentrated in a rotary evaporator. To remove the excess trifluoroacetic acid, the residue is twice taken up in toluene (20 ml) and concentrated. The title compound so obtained can be used in the next reaction step without further purification. $R_f$ 96: approximately 0.36 (silica gel, UV 366).

The starting material is prepared as follows:

**c) 3-methoxy-7β-[(2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-thiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenyl methyl ester**

A solution of 1.26 g (2.0 mmol) of the (2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-thiazol-4-yl)-acetic acid obtainable according to Example 17d) and 0.714 g (1.8 mmol) of 3-methoxy-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 20 ml of absolute tetrahydrofuran in the presence of 0.27 g of 1-hydroxybenzotriazole and 0.45 g of N,N'-dicyclohexyl carbodiimide is stirred at room temperature for 3.5 hours. The N,N'-dicyclohexylurea which is formed is filtered off and the filtrate is concentrated. The residue, dissolved in 60 ml of ethyl acetate, is then washed with 20 ml of each of ice-water, 1N hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution. After drying the organic phase with sodium sulphate and removing the solvent in a rotary evaporator, the residue is purified over silica gel with methylene chloride/ethyl acetate 1:1 as eluant to yield the title compound as an amorphous powder. $R_f$: approximately 0.46 (silica gel, UV 366, methylene chloride/ethyl acetate 1:1).

**d) (2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-thiazol-4-yl)-acetic acid**

2.45 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 1.74 g (5 mmol) of (2R,S)-2-amino-2-(2-(2,2,2-trichloroethoxycarbonylamino)-thiazol-4-yl)-acetic acid in 17 ml of absolute methylene chloride. Then, after cooling the reaction mixture to 0°, 0.4 ml of absolute pyridine and 1.42 g (5 mmol) of 2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonyl chloride are added. The reaction mixture is stirred for another 1½ hours at 0° and for 4 hours at room temperature, is then diluted with ethyl acetate (60 ml) and washed with 1N hydrochloric acid and saturated sodium chloride solution. After drying the organic phase over sodium sulphate and removing the solvent in a rotary evaporator, the crude product is purified over silica gel with ethyl acetate as eluant to yield the title compound as an amorphous beige powder. $R_f$ 96: approximately 0.75 (silica gel, UV 366).

The compounds obtained in Examples 13a), 13b), 14a), 14b), 15a) and 15b) can also be obtained according to the method described in Examples 17a) to 17d).

**Example 18**

**The sodium salt of 3-(1-carboxymethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

A slurry of 1.07 g (2 mmol) of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid and 0.64 g (4 mmol) of 1-carboxymethyl-5-mercapto-1H-tetrazole in 6 ml of water is adjusted to pH 7 by the addition of 1N sodium hydroxide solution. The clear solution is then stirred under nitrogen for 4 hours at 65°, cooled and introduced into 300 ml of ethanol. The precipitate which forms is filtered off, dissolved in a little water and purified over 25 g of silylated silica gel (Antec Opti-UPC 12) with water as eluant. After combining the fractions that are uniform according to thin-layer chromatography, the solvent is distilled off in a rotary evaporator. The residue is dried under a high vacuum to yield the title compound in the form of the dihydrate. M.p. above 150° (with decomposition); $R_f$: approximately 0.63 (silica gel Opti-UPC 12, UV 366, acetonitrile/water 1:9); UV: 251 (15000 in 0.1N HCl).

**Example 19**

**The sodium salt of 3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 18, the title compound is obtained in the form of the dihydrate starting from 1.07 g (2 mmol) of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid and 1.02 g (4 mmol) of the sodium salt of 1-sulphomethyl-5-mercapto-1H-tetrazole in 6 ml of water. M.p. above 180° (with decomposition); $R_f$: approximately 0.20 (silica gel Antec Opti-UPC 12, UV 366, water); UV: 252 (14900, 0.1N HCl).

**Example 20**

**3-[1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthiomethyl]-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 18, the title compound is obtained starting from 1.07 g (2 mmol) of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid and 0.69 g (4 mmol) of 1-N,N-dimethylaminoethyl-5-mercapto-1H-tetrazole in 6 ml of water. $R_f$: approximately 0.18 (silica gel Antec Opti-UPC 12, UV 366, acetonitrile/water 2:8).

**Example 21**

**a) The sodium salt of 7β-[(2R,S)-2-(2-methanesulphonylaminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

5.5 ml of trifluoroacetic acid are added to a solution of 1.13 g (1.4 mmol) of the 7β-[(2R,S)-2-(2-methanesulphonylaminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 21b) and 1.1 ml of anisole in 5.5 ml of absolute methylene chloride, the mixture is stirred for one hour at room temperature with the exclusion of moisture and then, at 0°, 60 ml of cold diethyl ether are added. The beige precipitate is filtered off, washed with a little diethyl ether and, after being dissolved in 20 ml of water, adjusted to pH 7 with 1N sodium hydroxide solution and extracted with 3×10 ml of ethyl acetate. The aqueous phase is concentrated to approximately 5 ml and purified over silylated silica gel (Antec Opti-UPC 12) with water as eluant. The fractions that are uniform according to thin-layer chromatography are combined, concentrated in a rotary evaporator and dried under a high vacuum to yield the title compound in the form of the dihydrate. M.p. above 175° (with decomposition); $R_f$ 96: approximately 0.30 (silica gel, UV 366); UV: 250 (10300, water).

**b) 7β-[(2R,S)-2-(2-methanesulphonylaminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

0.48 ml of absolute pyridine and then 0.5 ml of methanesulphonyl chloride are added while stirring with the exclusion of moisture to a solution of 4.0 g (5.5 mmol) of the 7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 21c) in 60 ml of absolute methylene chloride. After 4 hours, the reaction mixture is diluted with 300 ml of ethyl acetate and washed with 3×50 ml of saturated sodium chloride solution, dried over sodium sulphate and concentrated in a rotary evaporator. The residue is purified over silica gel (40 times the amount) with methylene chloride/ethyl acetate 1:1 as eluant to yield the title compound as a colourless, amorphous powder. $R_f$: approximately 0.28 (silica gel, UV 366, methylene chloride/ethyl acetate 1:1).

The starting material is prepared as follows:

**c) 7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

5.25 g of zinc dust are added in portions while stirring to a solution, cooled to 0°, of 5.25 g (5.8 mmol) of the 7β-[(2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according

to Example 21d) in 50 ml of acetic acid/acetonitrile (1:1). After a reaction period of one hour at room temperature, another 5 g of zinc dust are added, after a reaction period of 5 hours in all, the reaction mixture is diluted with 200 ml of ethyl acetate, the zinc dust is filtered off and the filtrate is washed with cold, saturated, aqueous sodium bicarbonate and sodium chloride solutions. After drying with sodium sulphate and removing the solvent in a rotary evaporator, the title compound is obtained and can be used in the next reaction step without further purification. $R_f$: approximately 0.58 (silica gel, UV 366).

**d) 7β[(2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 11.12 g (20 mmol) of the (2R,S)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid prepared according to Example 21e) and 7.3 g (20 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 200 ml of absolute tetrahydrofuran in the presence of 2.7 g of 1-hydroxybenzotriazole and 4.54 g of dicyclohexyl carbodiimide is stirred for 3 hours at room temperature. The dicylohexylurea which forms is then filtered off and the filtrate is concentrated. The residue, dissolved in ethyl acetate (300 ml), is washed with 1N hydrochloric acid, saturated sodium bicarbonate solution and saturated sodium chloride solution. After drying the organic phase with sodium sulphate, the solvent is removed in a rotary evaporator and the resulting crude product is purified over silica gel (40 times the amount) with methylene chloride/ethyl acetate 1:1 as eluant to yield the title compound as an amorphous powder. TLC (silica gel, identification UV: $R_f$ approximately 0.65 (methylene chloride/ethyl acetate 1:1).

**e) 7β-[(2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethylester**

0.38 g of *p*-toluenesulphonic acid monohydrate is added while stirring at room temperature to a solution of 0.828 g (1 mmol) of 7β-[(2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in 10 ml of absolute methylene chloride. After 5 hours, the reaction mixture is diluted with diethyl ether (30 ml) and washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. The organic phase is dried (sodium sulphate) and concentrated in a rotary evaporator. The title compound so obtained is identical to the product obtained according to Example 21c).

**Example 22**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.5 g of the 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 22d) are reacted in 7.5 ml of $CH_2Cl_2$ and 2.45 ml of anisole with 28 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 165° (with decomposition); $[\alpha]_D^{20°}=-9°\pm1°$ (0.80% in $H_2O$); IR: 3700—2500 (broad), 1762, 1685, 1603, 1521 (Nujol); UV: 260 (13600; $H_2O$).

**b) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.18 g of the 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 22e) are reacted in 4.5 ml of $CH_2Cl_2$ and 1.52 ml of anisole with 17.4 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 168° (with decomposition); $[\alpha]_D^{20°}=-22°\pm1°$ (0.96% in $H_2O$); IR: 3700—2500 (broad), 1762, 1685, 1602, 1521 (Nujol); UV 260 (3500; $H_2O$).

**c) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.42 g of the 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 22e) are reacted in 5 ml of $CH_2Cl_2$ and 1.69 ml of anisole with 19.3 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 168° (with decomposition); $[\alpha]_D^{20°}=+8°\pm1°$ (0.85% in $H_2O$); IR: 3700—2500 (broad), 1762, 1685, 1603, 1521 (Nujol); UV: 260 (13700, $H_2O$).

**d) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetic acid obtainable according to Example 22f) are reacted with 3.5 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in

40 ml of tetrahydrofuran (0.76 g of hydroxybenzotriazole; three times 0.7 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=-99°\pm1°$ (0.75% in $CHCl_3$); IR: 3400, 3300, 1780, 1720, 1695 (shoulder), 1600 (weak), 1525 ($CH_2Cl_2$); UV: 260 (16000; EtOH).

**e) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

The binary mixture of the two title compounds obtainable according to Example 22d) is chromatographed over 300 g of silica gel (graduated column; eluant: toluene/ethyl acetate 4:1, 7:3 and 1:1 mixtures). The title compound having the 2R-configuration is eluted first (see Example 7d) for assignment of configuration); $[\alpha]_D^{20°}=-126°\pm1°$ (0.75% in $CHCl_3$); IR: 3400, 3300, 1780, 1720, 1695 (shoulder), 1600 (weak), 1525 ($CH_2Cl_2$); UV: 260 (16100; EtOH).

The next fractions consist of a binary mixture of the (2R)- and (2S)-title compounds. Finally, the uniform (2S)-title compound is eluted; $[\alpha]_D^{20°}=-86°\pm1°$ (0.93% in $CHCl_3$); IR: 3400, 3300, 1780, 1720, 1695 (shoulder), 1600 (weak), 1525 ($CH_2Cl_2$); UV: 260 (16200; EtOH).

The starting material is prepared as follows:

**f) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetic acid**

Analogously to Example 6c), 5 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine are reacted in 45 ml of $CH_2Cl_2$ with 2.14 ml of mesyl chloride (15 ml of N,O-bis(trimethylsilyl)acetamide; 1.45 ml of pyridine), and worked up. The title compound is obtained and is further processed according to Example 22d) without being characterised.

**Example 23**

**3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

2.81 g of the sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (see Example 1a) for preparation), 0.95 g of isonicotinamide, 8.6 g of sodium iodide and 0.94 g of trichloroacetic acid are hreated in 5.75 ml of water for 1½ hours at 70°. The mixture is then cooled and introduced into 1 litre of ethanol. The precipitate which forms is filtered off, washed with ether and dried. It is then dissolved in a little water and the aqueous phase is extracted with 175 ml of each of liquid ion exchanger LA 1 (HOAC form), hexane and ethyl acetate (twice). The aqueous phase is then adjusted to pH 6.8 with 1N NaOH and concentrated *in vacuo*. The mixture is then adjusted to pH 2.2 with 1N hydrochloric acid and chromatographed over 100 g of silylated silica gel (Antec Opti-UPC 12), water/acetonitrile (95:5). The product-containing fractions are combined, concentrated to a volume of approximately 5 ml and introduced into 400 ml of ethanol. The product which precipitates is filtered off, washed with ethanol and diethyl ether and dried. The hydrate of the title compound is obtained; m.p. above 160° (with decomposition); $[\alpha]_D^{20°}=-3°\pm1°$ (0.78% in $H_2O$); IR: 2700—2500 (broad), 1779, 1688, 1610, 1568, 1522 (Nujol); UV: 260 (13600; $H_2O$).

**Example 24**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.7 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester which can be prepared according to Example 24b) are reacted in 4 ml of $CH_2Cl_2$ and 1.28 ml of anisole with 15 ml of trifluoroacetic acid, worked up and reprecipitated. The title compound is obtained; m.p. above 200° (with decomposition); $[\alpha]_D^{20°}=+98°\pm1°$ (0.84% in $H_2O$); IR: 3700—2600 (broad), 1760, 1650 (broad), 1600, 1521 (Nujol); UV: 251 (10200), 312 (1100; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.21 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetic acid which can be prepared according to Example 24c) are reacted with 1.9 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 20 ml of tetrahydrofuran (0.53 g of hydroxybenzotriazole; three times 0.46 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+23°\pm1°$ (0.80% in $CHCl_3$); IR: 3400, 3300, 1781, 1720, 1675, 1529 ($CH_2Cl_2$); UV: 258 (13600; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid are reacted in 24 ml of $CH_2Cl_2$ with 0.71 ml of acetyl chloride (10 ml of N,O-bis(trimethylsilyl)-acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed according to Example 24b) without being characterised.

**Example 25**

**a) The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.32 g of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 25b) are reacted in 3.2 ml of $CH_2Cl_2$ and 1 ml of anisole with 12 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. above 160° (with decomposition); $[\alpha]_D^{20°}=+61°\pm1°$ (0.79% in $H_2O$); IR: 3700—2500 (broad), 1762, 1680 (shoulder), 1605, 1624 (Nujol); UV: 258 (12700; EtOH).

**b) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 1.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetic acid (see Example 24c) for preparation) are reacted with 1.46 g of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 16 ml of tetrahydrofuran (0.4 g of hydroxybenzotriazole; three times 0.35 g of dicyclohexyl carbodiimide each time in 3 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+6°+1°$ (0.71% in $CHCl_3$); IR: 3400, 3300, 1787, 1725, 1695, 1677, 1540 $cm^{-1}$ ($CH_2Cl_2$); UV: 258 (14900; EtOH).

**Example 26**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.46 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 26b) are reacted in 3.2 ml of $CH_2Cl_2$ and 1.0 ml of anisole with 12 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. above 185° (with decomposition); $[\alpha]_D^{20°}=+79°\pm1°$ (0.91% in $H_2O$); IR: 3700—2500, 1760, 1680 (shoulder), 1640, 1600, 1577, 1525 (Nujol); UV: 230 (17300; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.39 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetic acid obtainable according to Example 26c) are reacted with 2 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 20 ml of tetrahydrofuran (0.56 g of hydroxybenzotriazole; three times 0.49 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+20°\pm1°$ (1.01% in $CHCl_3$); IR: 3400, 3300, 1785, 1720, 1665, 1602, 1520 ($CH_2Cl_2$); UV: 255 (11500; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid are reacted in 24 ml of tetrahydrofuran with 1.16 ml of benzoyl chloride (10 ml of N,O-bis-(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 27**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.9 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 10 ml of $CH_2Cl_2$ and 0.57 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 215° (with decomposition); $[\alpha]_D^{20°}=+101°\pm1°$ (1.22% in $H_2O$); IR: 3700—2500 (broad), 1760, 1670, 1600, 1520 (Nujol); UV: 252 (9900), 318 (200; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.3 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetic acid obtainable according to Example 27c) are reacted with 2.0 g

of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 30 ml of tetrahydrofuran (0.5 g of hydroxybenzotriazole; three times 0.4 g of dicyclohexyl carbodiimide each time in 6 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+18°\pm1°$ (0.99% in $CHCl_3$); IR: 3400, 3300, 1790, 1727, 1690, 1640, 1600, 1542 (Nujol); UV: 260 (13400; EtOH).

The starting material is prepared as follows:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid are reacted in 25 ml of tetrahydrofuran with 1.35 ml of the mixed anhydride of acetic acid and formic acid [prepared from acetic anhydride and formic acid; see, in that connection, G. Büchi *et al.*, JACS *93*, 2492 (1971)] (10 ml of N,O-bis(trimethylsilyl)-acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 28**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.17 g of the 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenyl methyl ester obtainable according to Example 28c) are reacted in 5.5 ml of $CH_2Cl_2$ and 0.29 ml of anisole with 8.2 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. above 165° (with decomposition); $[\alpha]_D^{20°}=-12°\pm1°$ (1.00% in $H_2O$); IR: 3700—2600 (broad), 1760, 1675, 1605, 1520 (Nujol); UV: 259 (13200; $H_2O$).

**b) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.1 g of the 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 28c) are reacted in 5.5 ml of $CH_2Cl_2$ and 0.29 ml of anisole with 8.2 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained: m.p. above 165° (with decomposition); $[\alpha]_D^{20°}=+7°\pm1°$ (1.09% in $H_2O$); IR: 2700—2600, 1762, 1672, 1605, 1524 (Nujol); UV: 259 (13500; $H_2O$).

**c) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetic acid (preparation according to Example 27c)) are reacted with 2.77 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 60 ml of tetrahydrofuran (0.65 g of hydroxybenzotriazole; three times 0.52 g of dicyclohexyl carbodiimide each time in 7 ml of tetrahydrofuran) and worked up. The resulting crude product is chromatographed over 300 g of silica gel (graduated column) (eluant: toluene/ethyl acetate 4:1, 2:1 and 1:1 mixtures and ethyl acetate). In so doing, the title compound having the 2R-configuration is eluted first. (See Example 7d) for configuration); $[\alpha]_D^{20°}=-83°\pm1°$ (0.85% in $CHCl_3$); IR: 3400, 3300, 1788, 1722, 1691, 1605, 1542 ($CH_2Cl_2$); UV: 260 (16800; EtOH).

The next fractions consist of a binary mixture of the above (2R)-compound with the (2S)-isomer.

The last fractions yield the title compound having the 2S-configuration; $[\alpha]_D^{20°}=-84°\pm1°$ (0.95% in $CHCl_3$); IR: 3400, 3300, 1789, 1722, 1691, 1605, 1542 ($CH_2Cl_2$): UV: 260 (17000; EtOH).

**Example 29**

**a) The sodium salt of 7β-[(2R,S)-2-(2-(2-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

20 ml of trifluoroacetic acid are added to a solution of 3.9 g (4 mmol) of 7β-[(2R,S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3.9 ml of anisole in 20 ml of methylene chloride, the mixture is stirred under a nitrogen atmosphere for one hour at 25° and then, at 0°, 300 ml of diethyl ether are added. The beige precipitate is filtered off, washed with a little diethyl ether and, after being dissolved in 30 ml of water, adjusted to pH 7 with 2N sodium hydroxide solution. After extraction with ethyl acetate, the aqueous phase is purified over silylated silica gel (Opti-UPC 12) with water as eluant. The title compound is obtained in the form of the dihydrate. M.p. above 170° (with decomposition); $R_f$ 0.38 (silica gel Opti-UPC 12, $H_2O/CH_3CN$, 8:2); $[\alpha]_D^{20°}=+89°\pm1°$ ($H_2O$; c=0.152%); UV: ($H_2O$): 251 ($\varepsilon$=15550).

**b) 7β-[(2R,S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 0.91 g (4.4 mmol) of N,N'-dicyclohexyl carbodiimide in 10 ml of absolute tetrahydrofuran and, after approximately 10 minutes, 1.46 g (4 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester are added while stirring at room temperature to a solution of 2.48 g (4 mmol) of the (2R,S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid obtainable according to Example 39c) and 0.54 g (4 mmol) of 1-hydroxybenzotriazole in 40 ml of absolute tetrahydrofuran. After a reaction period of 4 hours, the N,N'-dicyclohexylurea which precipitates is filtered off and the filtrate is concentrated in a rotary evaporator. The residue, dissolved in 400 ml of ethyl acetate, is washed twice with 50 ml of 1N hydrochloric acid and twice with 50 ml of saturated sodium chloride solution. The crude product obtained after drying over sodium sulphate and removing the solvent in a rotary evaporator is purified over 160 g of silica gel with methylene chloride/ethyl acetate (1:1) as eluant. The title compound is obtained; $R_f$ (silica gel, development with iodine): 0.33 ($CHCl_3/CH_2OH/CH_3COOH$ 75:22:3).

Preparation of the starting material:

**c) (2R,S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid**

3.4 g (16.5 mmol) of N,N'-dicyclohexyl carbodiimide are added while stirring at room temperature to a solution of 3.87 g (15 mmol) of 2-BOC-aminothiazol-4-yl-acetic acid and 2.03 g (15 mmol) of 1-hydroxybenzotriazole. After a reaction period of 15 minutes, 5.71 g (15 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid are added to the suspension formed. After a reaction period of 4 hours, the resulting N,N'-dicyclohexylurea is filtered off and the filtrate is concentrated in a rotary evaporator. The residue, dissolved in 500 ml of ethyl acetate, is washed three times with 1N hydrochloric acid and three times with saturated sodium chloride solution. The crude product obtained after drying over sodium sulphate and removing the solvent in a rotary evaporator is purified over 400 g of silica gel with methylene chloride/ethyl acetate 1:2 as eluant to yield the title compound as an amorphous powder.

**Example 30**

**a) 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-butyrylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as the 1.5-hydrate by reacting 3.1 g (3.9 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-butyrylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 3.1 ml of anisole with 15 ml of trifluoroacetic acid in 15 ml of absolute methylene chloride; m.p. above 170° (with decomposition); $R_f$ 96: approximately 0.43; $[\alpha]_D^{20°}=+86°\pm1°$ ($H_2O$, C=0.872%); UV ($H_2O$): 250 (ε=10700).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-butyrylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained by reacting 3.4 g (7.5 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-butyrylamino)-ethanesulphonylamino)-acetic acid with 2.75 g (7.5 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.01 g of 1-hydroxybenzotriazole and 1.7 g of N,N'-dicyclohexyl carbodiimide in 80 ml of tetrahydrofuran; $R_f$ (silica gel): 0.45 (ethyl acetate).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-butyrylamino)-ethanesulphonylamino)-acetic acid**

10 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 3.80 g (10 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 90 ml of absolute tetrahydrofuran. After a reaction period of one hour at 65°, the reaction mixture is cooled to 0°, 0.88 ml of pyridine and 1.14 ml of butyryl chloride, dissolved in 10 ml of tetrahydrofuran, are added and the whole is stirred at room temperature for a further 15 hours. After removing the solvent, the residue is taken up in ethyl acetate and washed four times with 50 ml of 0.5N hydrochloric acid and four times with 50 ml of saturated sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator to yield the title compound which can be used in the next reaction step without further purification.

**Example 31**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.84 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloyl-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester

obtainable according to Example 31b) are reacted in 4.14 ml of $CH_2Cl_2$ and 1.34 ml of anisole with 15.5 ml of trifluoroacetic acid worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 190° (with decomposition); IR: 3700—2600 (broad), 1760, 1660, 1600, 1522 (Nujol); UV: 255 (10000; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.88 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloyl-aminoethanesulphonylamino)-acetic acid obtainable according to Example 31c) are reacted with 2.2 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 20 ml of tetrahydrofuran (0.66 g of hydroxybenzotriazole; three times 0.58 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+26°\pm1°$ (1.01% in $CHCl_3$); IR: 3400, 2200, 1778, 1715, 1675, 1625, 1605 (shoulder), 1515 ($CH_2Cl_2$); UV: 257 (3400; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethane-sulphonylamino)-acetic acid are reacted in 24 ml of tetrahydrofuran with 0.81 ml of acryloyl chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 32**

**a) The sodium salt of 7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethane-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.4 g of the 7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 32c) are reacted in 7.4 ml of $CH_2Cl_2$ and 0.4 ml of anisole with 11.2 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. decomposition from 200°; $[\alpha]_D^{20°}=+107°\pm1°$ (0.85% in $H_2O$); IR: 3700—2600, 1769, 1670 (shoulder), 1645, 1600, 1530 (Nujol); UV: 255 (11000; $H_2O$).

**b) The sodium salt of 7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethane-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1 g of the 7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyclopropyl-carbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 32c) are reacted in 5.3 ml of $CH_2Cl_2$ and 0.28 ml of anisole with 8 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. decomposition from 200°; $[\alpha]_D^{20°}=+77°\pm1°$ (0.56% in $H_2O$); IR: 3700—2500 (broad), 1760, 1670 (shoulder), 1645, 1600, 1525 (Nujol); UV: 255 (9600), 315 (600; $H_2O$).

**c) 7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, and 7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.4 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyclopropyl-carbonylaminoethanesulphonylamino)-acetic acid obtainable according to Example 32d) are reacted with 1.93 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 30 ml of tetrahydrofuran (0.54 g of hydroxybenzotriazole; three times 0.46 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran) and worked up. The resulting crude product is chromatographed over 300 g of silica gel (graduated column) (eluant: toluene/ethyl acetate 2:1). In so doing, the title compound having the (2R)-configuration is eluted first; $[\alpha]_D^{20°}=+2°\pm1°$ (0.95% in $CH_2Cl_2$); IR: 3300, 1791, 1730, 1700, 1670, 1640, 1602, 1540 ($CH_2Cl_2$); UV: 258 (12500; EtOH).

The next fractions consist of a binary mixture of the (2R)- and (2S)-title compounds.

Finally, the (2S)-title compound is obtained; $[\alpha]_D^{20°}=+38°\pm1°$ (0.85% in $H_2O$); IR: 3400, 3300, 1792, 1739, 1704, 1670, 1640, 1602, 1540 ($CH_2Cl_2$); UV: 257 (11900; EtOH).

Preparation of the starting material:

**d) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethanesulphonyl-amino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethane-sulphonylamino)-acetic acid are reacted in 24 ml of tetrahydrofuran with 0.875 ml of cyclopropane-carboxylic acid chloride (16 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 33**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate by reacting 2.23 g (2.8 mmol) of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 33b) in the presence of 2.2 ml of anisole with 11 ml of trifluoroacetic acid; m.p. above 168° (with decomposition); $R_f$ (silica gel Opti-UPC 12): approximately 0.35 ($H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as an amorphous powder by reacting 2.91 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetic acid with 2.38 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.88 g of 1-hydroxybenzotriazole and 1.48 g of N,N'-dicyclohexyl carbodiimide in 60 ml of absolute tetrahydrofuran; $R_f$ (silica gel): approximately 0.18 (methylene chloride/ethyl acetate 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetic acid**

10 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 3.8 g (10 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 100 ml of absolute tetrahydrofuran. After a reaction period of one hour at 65°, the reaction mixture is cooled to 0°, 0.96 ml of pyridine and 1.0 ml of cyanoacetic acid chloride are added and the whole is then stirred for 3 hours at room temperature. After removing the solvent, the residence is taken up in ethyl acetate and washed four times with 0.5N hydrochloric acid and four times with saturated sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator. The title compound is obtained and is used in the next reaction step without being purified.

**Example 34**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester which can be prepared according to Example 34b) are reacted in 8 ml of $CH_2Cl_2$ and 0.9 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. decomposition above 150°; $[\alpha]_d^{20°}=+93°\pm1°$ (1.22% in $H_2O$); IR: 3700—2600 (broad), 1760, 1665, 1600, 1525 (Nujol); UV: 252 (9600; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3.6 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetic acid obtainable according to Example 36c) are reacted with 2.9 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 40 ml of tetrahydrofuran, (1 g of hydroxybenzotriazole; three times 0.53 g of dicyclohexyl carbodiimide each time in 7 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+19°\pm1°$ (1.16% in $CHCl_3$); IR: 3400, 3300, 1790, 1728, 1692, 1640 (shoulder), 1600, 1530 ($CH_2Cl_2$); UV: 260 (14000; EtOH).

The starting material is prepared as follows:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid are reacted in 25 ml of tetrahydrofuran with 0.92 ml of methoxyacetyl chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 35**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.3 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 7 ml of $CH_2Cl_2$ and 0.37 ml of anisole with 10.6 ml of trifluoroacetic acid, worked up and

reprecipitated. The hydrate of the title compound is obtained; m.p. decomposition from 220°; $[\alpha]_D^{20°}=+91°\pm1°$ (1.00% in $H_2O$); IR: 3700—2700 (broad), 2120, 1760, 1675 (shoulder), 1645, 1600, 1522 (Nujol); UV: 249 (9700), 314 (700; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3.1 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 35c) are reacted with 0.258 ml of propiolic acid in 45 ml of tetrahydrofuran (0.56 g of hydroxybenzotriazole; three times 0.29 g of dicyclohexyl-carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; IR: 3400, 3300, 2120, 1790, 1726, 1700 (shoulder), 1668, 1603, 1540, ($CH_2Cl_2$); UV: 258 (13800; EtOH).

Preparation of the starting material:

**c) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

12.9 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,2,2-trichloroethoxycarbonyl-amino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 35d) are stirred for 3 hours at 0° with 14 g of zinc dust in 150 ml of acetonitrile/acetic acid 1:1 mixture. The zinc residue is then filtered off, and the filtrate is washed with acetonitrile and concentrated to dryness by evaporation *in vacuo*. The evaporation residue is taken up in 0.5 litre of ethyl acetate/water 1:1 mixture, adjusted to pH 8 with 1N sodium hydroxide solution, diluted with a little ethyl acetate and washed neutral with saturated aqueous NaCl solution. The mixture is then dried over $Na_2SO_4$, concentrated by evaporation *in vacuo* and the crude product is reprecipitated once from $CH_2Cl_2$/ether/hexane. The title compound is obtained; $[\alpha]_D^{20°}=+29°\pm1°$ (1.09% in $CHCl_3$); IR: 3450—2600 (broad), 1770, 1715, 1690 (shoulder), 1640, 1532 ($CH_2Cl_2$); UV: 258 (11800; EtOH).

**d) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 11.8 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,2,2-trichloro ethoxycarbonylamino)-ethanesulphonylamino)-acetic acid are reacted with 7.05 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 100 ml of tetrahydrofuran (1.95 g of hydroxybenzotriazole; three times 1.7 g of dicyclohexyl carbodiimide each time in 20 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+14°\pm1°$ (0.90% in $CHCl_3$): IR: 3400, 3300, 1781, 1720, 1700 (shoulder), 1635, 1520 ($CH_2Cl_2$); UV: 258 (13600; EtOH).

**Example 36**

**a) The sodium salt of 7β-[(2R,S)-2-(2-((2R)-2-amino-2-carboxyethoxycarbonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate by reacting 1.5 g (1.35 mmol) of 7β-[(2R,S)-2-(2-((2R)-2-BOC-amino-2-diphenylmethoxycarbonyl-ethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 1.5 ml of anisole and 7.5 ml of trifluoroacetic acid in 7.5 ml of methylene chloride; m.p. above 151°; $R_f$ (silica gel Opti-UPC 12): approximately 0.75 (water/acetonitrile 9:1); $[\alpha]_D^{20°}=+68°\pm1°$ (0.659% in 0.1N HCl); UV: (in 0.1N HCl): 252 (ε=12900).

**b) 7β-[(2R,S)-2-(2-((2R)-2-BOC-amino-2-diphenylmethoxycarbonylethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a yellowish powder by reacting 1.56 g (2 mmol) of (2R,S)-2-(2-((2R)-2-BOC-amino-2-diphenylmethoxycarbonylethoxycarbonyl-amino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 0.73 g (2 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.27 g of 1-hydroxy-benzotriazole and 0.45 g of N,N'-dicyclohexyl carbodiimide in 30 ml of tetrahydrofuran; $R_f$: approximately 0.63 (methylene chloride/ethyl acetate 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-((2R)-2-BOC-amino-2-diphenylmethoxycarbonylethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid**

5.0 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 1.9 g (5 mmol) of (2R,S)-2-(2-aminoethane-sulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 60 ml of absolute tetrahydrofuran. After a reaction period of one hour at 60°, the reaction mixture is cooled to room temperature, 0.4 ml of pyridine and 2.17 g of (2R)-2-BOC-amino-2-diphenylmethoxycarbonylethoxycarbonyl chloride are

added and the whole is then stirred for 2 hours. After removing the solvent, the residue is taken up in 250 ml of ethyl acetate and washed three times with 0.1N hydrochloric acid and three times with saturated sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator and the residue is purified over silica gel with methylene chloride/ethyl acetate 1:1 as eluant to yield the title compound as an amorphous powder; $R_f$ (silica gel): approximately 0.58 (chloroform/methanol/glacial acetic acid 75:22:3).

**Example 37**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-ethoxycarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as the 1.5-hydrate by reacting 4.2 g (5.25 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-ethoxycarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 4.2 ml of anisole and 20 ml of trifluoroacetic acid in 20 ml of methylene chloride; m.p. above 168° (with decomposition); $[\alpha]_D^{20°}=+95°\pm1°$ (1.027% in water); UV (water): 251 ($\varepsilon$=10500).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-ethoxycarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as an amorphous powder by treating 3.8 g (8.4 mmol) of (2R,S)-2-(2-ethoxycarbonylaminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 3.08 g (8.4 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.13 g of 1-hydroxybenzotriazole and 1.90 g of N,N'-dicyclohexyl carbodiimide; $R_f$ (silica gel): approximately 0.58 (ethyl acetate).

Preparation of the starting material:

**c) (2R,S)-2-(2-ethoxycarbonylaminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid**

10 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 3.8 g (10 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 90 ml of absolute tetrahydrofuran. After a reaction period of one hour at 65°, the reaction mixture is cooled to 0°, 0.90 ml of pyridine and 1.05 ml of chloroformic acid ethyl ester are added and the whole is then stirred for 4 hours at room temperature. After removing the solvent, the residue is taken up in ethyl acetate and washed four times with 0.5N hydrochloric acid and four times with saturated sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator. The title compound is obtained and can be used in the next reaction step without further purification.

**Example 38**

**a) The sodium salt of 7β-[(2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the 1.5-hydrate of the title compound is obtained as a yellowish powder by reacting 2.0 g (2.19 mmol) of 7β-[(2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.0 ml of anisole with 10 ml of trifluoroacetic acid in 10 ml of methylene chloride; m.p. above 175° (with decomposition); $[\alpha]_D^{20°}=+79°\pm1°$ (0.066% in water); UV (water): 257 ($\varepsilon$=19200); $R_f$ (silica gel): approximately 0.50.

**b) 7β-[(2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as an amorphous powder by treating 3.4 g (6.0 mmol) of (2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetic acid with 2.2 g (6.0 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.81 g of 1-hydroxybenzotriazole and 1.36 g of N,N'-dicyclohexyl carbodiimide in 60 ml of tetrahydrofuran; $R_f$ (silica gel): approximately 0.58 (methylene chloride/ethyl acetate 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetic acid**

20 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 7.61 g (20 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 200 ml of absolute tetrahydrofuran. After one hour at 65°, the reaction mixture is cooled to 0°, 2.4 ml of pyridine and 6.65 g of 4-nitrobenzenesulphonyl chloride are added and the whole is then stirred at room temperature for 4 hours. After removing the solvent, the residue is taken up in 250 ml of ethyl acetate and washed four times with

0.5N hydrochloric acid and 4 times with saturated sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator. The crude product is chromatographed over 350 g of silica gel with methylene chloride/ethyl acetate (4:1) mixture as eluant. The title compound is obtained as an amorphous powder.

**Example 39**

**a) The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as a pale yellowish powder by reacting 6.8 g (6.9 mmol) of 3-acetoxymethyl-7β-[(2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in 6.8 ml of anisole with 6.8 ml of trifluoroacetic acid in 68 ml of methylene chloride; m.p. above 155° (with decomposition); $R_f$ (silica gel Opti-UPC 12): approximately 0.23 (water/acetonitrile 4:1); $[\alpha]_D^{20°}=+2°\pm1°$ (0.858% in water); UV (water): 258 ($\varepsilon$=23300).

**b) 3-acetoxymethyl-7β-[(2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a pale yellow powder by treating 10.18 g (18 mmol) of (2R,S)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetic acid with 7.9 g (18 mmol) of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.43 g of 1-hydroxybenzotriazole and 4.1 g of N,N'-dicyclohexyl carbodiimide in 150 ml of tetrahydrofuran; $R_f$ (silica gel): approximately 0.53 (methylene chloride/ethyl acetate 1:1).

**Example 40**

**a) The sodium salt of 7β-[(2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the dihydrate of the title compound is obtained as a yellowish powder by reacting 2.0 g (2.1 mmol) of 7β-[(2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.0 ml of anisole with 10 ml of trifluoroacetic acid in 10 ml of methylene chloride; m.p. above 150° (with decomposition); $[\alpha]_D^{20°}=+78°\pm1°$ (0.59% in water); $R_f$: approximately 0.30 (silica gel Opti-UPC 12, water/acetonitrile 4:1); UV: 245 (31500 in water).

**b) 7β-[(2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a pale yellow, amorphous powder by treating 2.0 g (3.3 mmol) of (2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 2.0 g of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.44 g of 1-hydroxybenzotriazole and 0.74 g of N,N'-dicylohexyl carbodiimide in 40 ml of tetrahydrofuran; $R_f$ (silica gel): approximately 0.48 (methylene chloride/ethyl acetate 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazole-4-yl)-acetic acid**

10 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 3.80 g (10 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 100 ml of absolute tetrahydrofuran. After a reaction period of one hour at 65°, the reaction mixture is cooled to 0° 1.2 ml of pyridine and 4.0 g of 2,4-dinitrobenzenesulphonyl chloride are added and the whole is then stirred at room temperature for 4 hours. After removing the solvent, the residue is taken up in 250 ml of ethyl acetate and washed four times with 0.5 N hydrochloric acid and four times with saturated sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator. The crude product is purified over 250 g of silica gel with methylene chloride/ethyl acetate (4:1) mixture as eluant. The title compound is obtained as an amorphous powder.

**Example 41**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanomethanesulphonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 0.5 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyanomethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 2 ml of $CH_2Cl_2$ and 0.2 ml of anisole with 5 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. decomposition from 220°; IR: *inter alia* 2374, 1755 (Nujol); UV: 251 (9700), 320 (650; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyanomethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.2 of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyanomethanesulphonylaminoethanesulphonylamino)-acetic acid are reacted with 0.6 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 25 ml of tetrahydrofuran (0.6 g of hydroxybenzotriazole; three times 0.3 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; IR: 3400, 3300, 2775, 1779, 1710, 1660, 1520 ($CH_2Cl_2$); UV: 259 (3200; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-cyanomethanesulphonylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid are reacted in 25 ml of tetrahydrofuran with 1.5 ml of cyanomethylsulphonyl chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 42**

**a) 7β-[(2R,S)-2-(2-methylaminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

3.4 g of the 7β-[(2R,S)-2-(2-methylaminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 42b) are dissolved in 10 ml of methylene chloride, and 1.3 ml of anisole and 62 ml of trifluoroacetic acid are added in succession to the solution and the whole is then stirred at room temperature for one hour with the exclusion of atmospheric moisture. A voluminous precipitate forms in the initially clear solution. The suspension is then poured into an ice-cold mixture of petroleum ether (600 ml) and diethyl ether (300 ml), the resulting trifluoroacetate is filtered off with suction, washed with petroleum ether and dried at room temperature under a high vacuum. The crude trifluoroacetate salt is then dissolved in 20 ml of ethanol/water (1:1) mixture, the solution is cooled to +5° and, while stirring and cooling, adjusted to a pH value of 5.0 by adding dropwise 2N sodium hydroxide solution. The solution is then poured into 600 ml of ethanol and concentrated to a volume of approximately 100 ml at 50° in a rotary evaporator. This operation is repeated twice with 300 ml of ethanol being added each time, the amorphous product being precipitated. The precipitate is filtered off with suction, washed in succession with ethanol, a mixture of ethanol/diethyl ether and diethyl ether. The hydrate of the title compound is obtained; m.p. decomposition from 190°; $[\alpha]_D^{20°}=+91°\pm1°$ (1.138% in 0.1N HCl); IR: 3320 (broad), 3195, 3120, 1775 (shoulder), 1765, 1690 (shoulder), 1680 (shoulder), 1670, 1640 (shoulder), 1615 (broad), 1520, 1380, 1350, 1150, 1120 (shoulder) (in Nujol); $R_f$ (silica gel): 0.23 (n-butanol-pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-methylaminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

3.2 g of zinc dust are added while stirring to a solution of 5.7 g of 7β-[(2R,S)-2-(2-N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazole-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in 100 ml of acetonitrile/acetic acid (1:1) mixture and the whole is stirred vigorously at room temperature for 3 hours. The suspension is then filtered through Celite®, the filtration residue is washed again with acetonitrile and the filtrate is concentrated to a volume of approximately 20 ml at 45° in a rotary evaporator. The solution is diluted with ethyl acetate, washed several times in succession with water and 1N sodium bicarbonate solution (pH 8), dried over sodium sulphate and concentrated at 45° in a rotary evaporator. The crude product is purified by chromatography over 25 times the amount of silica gel. Eluant: methylene chloride/methanol (97:3). In so doing, the title compound is obtained as a foam; $R_f$ (silica gel): approximately 0.45 (methylene chloride/methanol 9:1); IR: 3280 (broad), 1785, 1720, 1690 (shoulder), 1635, 1545, 1380 (shoulder), 1370, 1330, 1185, 1145 (in Nujol).

**c) 7β-[(2R,S)-2-(2-(N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 4.50 g of (2R,S)-2-[2-(N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino]-2-(2-BOC-aminothiazol-4-yl)-acetic acid, 2.58 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester and 0.65 g of 1-hydroxybenzotriazole in 52 ml of tetrahydrofuran is cooled to +2°, a solution of 0.82 g of N,N'-dicyclohexyl carbodiimide in 7 ml of tetrahydrofuran is added dropwise in the course of 10 minutes and the reaction mixture is stirred in an ice bath. After 3 hours, a further solution of 0.82 g of N,N'-dicyclohexyl carbodiimide in 7 ml of tetrahydrofuran is added dropwise to the reaction mixture. After stirring at 0° for 6 hours in all, the suspension is filtered off with suction, the residue is washed with ethyl acetate, the filtrate is diluted with ethyl acetate, washed several times with 1N sodium bicarbonate solution and water, dried over sodium sulphate and

concentrated at 45° in a rotary evaporator. The crude product is purified by chromatography over 20 times the amount of silica gel. Eluant: methylene chloride with from 2 to 5% of methyl acetate. The title compound is obtained as a foam. TLC (silica gel; identification: UV 366): $R_f$ approximately 0.60 (double spot diastereoisomeric mixture, toluene/ethyl acetate 1:1); IR: 3280 (broad), 1790, 1725, 1690 (shoulder), 1640 1565 (shoulder), 1550, 1380, 1335, 1190, 1155 (Nujol).

Preparation of the starting material:

**d) (2R,S)-2-[2-(N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino]-2-(2-BOC-aminothiazol-4-yl)-acetic acid**

18.5 ml of N,O-bis(trimethylsilyl)acetamide are added to a suspension of 5.0 g of (2R,S)-2-amino-2-(2-BOC-aminothiazol-4-yl)-acetic acid in 80 ml of acetonitrile/methylene chloride 1:1 mixture and the whole is stirred at room temperature with the exclusion of moisture, the acid slowly dissolving. After stirring for one hour, the clear solution is cooled to 0° and 4.0 ml of absolute pyridine are added. A solution of 9.0 g of 2-(N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonyl chloride in 20 ml of methylene chloride is added dropwise in the course of 30 minutes while stirring and cooling and the reaction mixture is stirred at room temperature for 1.5 hours. The suspension is then diluted with ethyl acetate, concentrated slightly, washed twice with 30 ml of 1N hydrochloric acid (pH approximately 2) each time and twice with sodium carbonate solution, dried over sodium sulphate and concentrated at 50° in a rotary evaporator. The crude product is purified by chromatography over 20 times the amount of silica gel. Eluant: methylene chloride with from 10 to 30% of methyl acetate. The title compound is obtained as a foam. TLC (silica gel; identification: UV 366 nm): $R_f$: 0.48 (methylene chloride/methanol 4:1) IR: 3200 (broad), 1715 (broad), 1680 (shoulder), 1540, 1370, 1325, 1185, 1145 (in methylene chloride).

**e) 2-(N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonyl chloride**

A suspension of 50 g of 2-methylaminoethanesulphonic acid (prepared as prescribed by B. Josephsch, Biochemische Zeitschrift, Berlin, *265*, 448 (1933)—CA *28*: 7909 (1934)) in 1400 ml of pyridine is cooled to +10°. 50 ml of chloroformic acid 2,2,2-trichloroethyl ester are added dropwise in the course of 40 minutes while stirring vigorously and cooling at from +10 to +15°, and the mixture is stirred at room temperature for 18 hours. The suspension is then filtered with suction through Celite® and the residue is washed with pyridine. The filtrate is concentrated at 55° in a rotary evaporator, toluene is added several times to the oily residue, with the pyridinium salt of 2-(N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonic acid crystallising out. The crystals are mixed with petroleum ether, filtered off with suction and washed with petroleum ether. M.p. 77—85° (with decomposition).

38 g of phosphorus pentachloride are added in portions in the course of 30 minutes while stirring vigorously at room temperature to a solution of 76 g of the pyridinium salt of 2-(N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonic acid in 380 ml of chloroform, the temperature rising to 35—40° with the evolution of hydrogen chloride. The reaction mixture is then heated under reflux for 3 hours, the solution is cooled to +5°, diluted with 200 ml of benzene, washed with 150 ml of ice-cold water, dried over sodium sulphate and concentrated at 55° in a rotary evaporator. The remaining, semi-solid mass is mixed with 300 ml of diethyl ether, the crystals which form (by-product) are filtered off with suction and the residue is washed with a little diethyl ether. The filtrate is concentrated at 55° in a rotary evaporator. The oily 2-(N-methyl-2,2,2-trichloroethoxycarbonylamino-ethanesulphonyl chloride remains. IR: 1715, 1620 (shoulder), 1370, 1180, 1160 (methylene chloride).

**Example 43**

**a) 7β-[(2R,S)-2-(2-methoxyethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 42a), the hydrate of the title compound is obtained by treating 1.8 g of 7β-[(2R,S)-2-(2-methoxyethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester (prepared according to Example 42b)) with 50 ml of trifluoroacetic acid and 0.8 ml of anisole in 5 ml of methylene chloride; m.p. above 180° (with decomposition); $[\alpha]_D^{20°} = +96° \pm 1°$ (1.955% in $H_2O$); IR: 3320 (broad), 3210, 1775 (shoulder), 1765 (broad), 1705 (shoulder), 1680, 1605, 1520, 1375, 1365, 1160, 1145 (in Nujol); TLC (silica gel; identification: UV 366 nm); $R_f$ 0.39 (n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-methoxyethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

The title compound is obtained by reacting 3.0 g of (2R,S)-2-(2-methoxyethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 2.6 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.55 g of 1-hydroxybenzotriazole and 1.54 g of N,N'-dicyclohexyl carbodiimide in 45 ml of tetrahydrofuran. The crude product is purified over 20 times the amount of silica gel. Eluant: methylene chloride/methyl acetate (9:1). TLC (silica gel; identification: UV

366 nm); $R_f$=0.58 (double spot diastereoisomeric mixture, system: toluene/chloroform/ethyl acetate/ethanol 32:32:32:5).

Preparation of the starting material:

**c) (2R,S)-2-(2-methoxyethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid**

11 ml of 2N sodium hydroxide solution are added to a solution of 5.4 g of (2R,S)-2-(2-methoxyethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid methyl ester in 45 ml of methanol and the mixture is stirred at room temperature. After a reaction period of 2.5 hours, a further 6 ml of 2N sodium hydroxide solution are added. After a reaction period of 5 hours in all, the pH value of the clear solution is adjusted to 7.5 by adding dropwise 1N hydrochloric acid and the majority of the methanol is evaporated off at 50° in a rotary evaporator. The aqueous solution is then cooled to 0°, covered with a layer of ethyl acetate, while stirring acidified (pH 2.5—3.0) by adding 20% aqueous citric acid and extracted twice with ethyl acetate. The organic extracts are combined, washed twice with a little sodium carbonate solution, dried over sodium sulphate and concentrated at 50° in a rotary evaporator. The crude product is purified by chromatography over 20 times the amount of silica gel. Eluant: methylene chloride with from 30 to 40% of methyl acetate. In so doing, the title compound is obtained as a yellow foam. TLC (silica gel; identification: UV 366 nm): $R_f$: 0.47 (n-butanol/glacial acetic acid/water 67:10:23); IR: 3320 (broad), 3300 (shoulder), 2950, 1770 (shoulder), 1730, 1570 (shoulder), 1550, 1390, 1370, 1140, 1110 (in methylene chloride).

**d) (2R,S)-2-(2-methoxyethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid methyl ester**

A solution of 5.0 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine methyl ester in 40 ml of dioxan and 10 ml of N-methylmorpholine is cooled to +2°. A solution of 30 ml of 2-methoxyethanesulphonyl chloride (prepared as prescribed by A. S. Matlack, J. Org. Chem., *23*, 729 (1958)) in 20 ml of dioxan is added dropwise in the course of 20 minutes while stirring and cooling, and the reaction mixture is stirred at room temperature for 2.5 hours. The suspension is concentrated to half its volume at 50° in a rotary evaporator, diluted with ethyl acetate, washed with water, 20% aqueous citric acid (pH~3) and again three times with a little water, and dried over sodium sulphate. After evaporating off the solvent at 50° in a rotary evaporator, the title compound remains behind as a yellow foam. TLC (silica gel; identification: UV 366 nm): $R_f$: 0.54 (toluene/chloroform/ethyl acetate/ethanol 32:32:32:5). IR: 3390, 3260, 1740 (shoulder), 1720, 1535, 1370, 1330, 1185 (shoulder), 1125 (in methylene chloride).

**Example 44**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 4.3 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 20 ml of $CH_2Cl_2$ and 1.4 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 230° (with decomposition); $[\alpha]_D^{20°}$=+99°±1° (0.90% in $H_2O$); IR: 3700—2500, 2260, 1755, 1675, 1600, 1520 (Nujol); UV: 250 (9200), 320 (700; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3.9 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetic acid are reacted with 3.8 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 45 ml of tetrahydrofuran (1.35 g of hydroxybenzotriazole; three times 0.66 g of dicyclohexyl carbodiimide each time in 8 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}$=+14°±1° (0.92% in $CHCl_3$); IR: 3400, 3300, 2260 (weak), 1780, 1720, 1700, 1635, 1530 ($CH_2Cl_2$); UV: 259 (14000; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetic acid**

Analogously to Example 6c), 3.4 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetic acid are reacted in 30 ml of $CH_2Cl_2$ with 2.6 g of cyanomethylsulphonyl chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 1.0 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 45**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-((3R)-3-amino-3-carboxypropionylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.1 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-((3R)-3-BOC-amino-3-tert.-butoxycarbonylpropionylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 7.5 ml of $CH_2Cl_2$ and 5 ml of anisole with 60 ml of

trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. above 210° (with decomposition); $[\alpha]_D^{20°}=+89°\pm1°$ (0.84% in $H_2O$); IR: 3700—2500 (broad), 1760, 1640, 1600, 1520 (Nujol); UV: 252 (9200), 316 (660; $H_2O$).

**b) The sodium salt of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-((3R)-3-BOC-amino-3-tert.-butoxycarbonylpropionylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 6b), 0.5 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester (see Example 35c) for preparation) is reacted with 0.22 g of (3R)-3-BOC-amino-3-tert.-butoxycarbonyl-propionic acid in 2.5 ml of tetrahydrofuran (70 mg of hydroxybenzotriazole; three times 60 mg of dicyclohexyl carbodiimide each time in 0.5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+32°\pm1°$ (0.96% in $CHCl_3$); IR: 3400, 3280, 1780, 1705, 1675, 1530 ($CH_2Cl_2$); UV: 257 (14000; EtOH).

**Example 46**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-pivaloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.62 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-pivaloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 3.6 ml of $CH_2Cl_2$ and 1.13 ml of anisole with 13.5 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. about 144° (with decomposition); $[\alpha]_D^{20°}=+92°\pm1°$ (0.69% in $H_2O$); IR: 3700—2700 (broad), 1755, 1675 (shoulder), 1657, 1616, 1522 (Nujol); UV: 250 (9700; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-pivaloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.06 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-pivaloylamino-ethanesulphonylamino)-acetic acid are reacted with 1.6 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 17 ml of tetrahydrofuran (0.45 g of hydroxybenzotriazole; three times 0.39 g of dicyclohexyl carbodiimide each time in 3.4 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+20°\pm1°$ (0.69% in $CHCl_3$); IR: 3450, 3400, 3280, 1780, 1715, 1695, 1650, 1520 $cm^{-1}$ ($CH_2Cl_2$); UV: 258 (14000; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-pivaloylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 8.5 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethane-sulphonylamino)-acetic acid are reacted in 30 ml of tetrahydrofuran with 1.56 ml of pivaloyl chloride (12.5 ml of N,O-bis(trimethylsilyl)acetamide; 1.03 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 47**

**a) 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-((2R)-2-amino-2-phenylacetamido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.1 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-((2R)-2-BOC-amino-2-phenylacetamido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 10 ml of $CH_2Cl_2$ and 0.57 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 240° (with decomposition); $[\alpha]_D^{20°}=+57°\pm1°$ (0.97% in $H_2O$); IR: 3700—2500 (broad), 1760, 1670, 1600, 1522 (Nujol); UV: 251 (9200), 320 (1000; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-((2R)-2-BOC-amino-2-phenylacetamido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 1 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethane-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester (see Example 35c) for preparation) are reacted with 0.34 g of N-BOC-(D)-phenylglycine in 15 ml of tetrahydrofuran (0.18 g of hydroxybenzotriazole; three times 0.09 g of dicyclohexyl carbodiimide each time in 2 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=-3°C\pm1°$ (0.99% in $CHCl_3$); IR: 3400, 3300, 1790, 1725, 1680, 1639, 1600, 1541 $cm^{-1}$ ($CH_2Cl_2$); UV: 258 (13100; EtOH).

**Example 48**

**a) 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminoacetamido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.9 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2-BOC-aminoacetamido)ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl

ester are reacted in 10 ml of $CH_2Cl_2$ and 0.57 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 230° (with decomposition); $[\alpha]_D^{20°}=+78°\pm1°$ (0.92% in HCOOH); IR: 3700—2500, 1765, 1685, 1654, 1611, 1542, 1529 $cm^{-1}$ (Nujol); UV: 252 (9500), 318 (300; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2-BOC-aminoacetamido)-ethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3.1 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-amino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester (see Example 35c) for preparation) are reacted with 0.74 g of N-BOC-glycine in 45 ml of tetrahydrofuran (0.56 g of hydroxybenzotriazole; three times 0.29 g of dicyclohexyl carbodiimide each time in 6 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+24°\pm1°$ (1.00% in $CHCl_3$); IR: 3400, 3300, 1790, 1725, 1690, 1640, 1542 $cm^{-1}$ ($CH_2Cl_2$); UV: 259 (14000; EtOH).

**Example 49**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxalylaminoethane-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.7 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyalylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenyl-methyl ester reacted in 8 ml of $CH_2Cl_2$ and 0.43 ml of anisole with 12 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 200° (with decomposition); $[\alpha]_D^{20°}=+73°\pm1°$ (0.89% in $H_2O$); IR: 3700—2600 (broad), 1760, 1685, 1600, 1525 (Nujol).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxalylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3.2 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxalyl-aminoethanesulphonylamino)-acetic acid are reacted with 2.48 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 26.2 ml of tetrahydrofuran (0.69 g of hydroxybenzotriazole; three times 0.6 g of dicyclohexyl carbodiimide each time in 5.2 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+17°\pm1°$ (0.84% in $CHCl_3$); IR: 3400, 3300, 1788, 1725, 1705, 1637, 1602, 1540 ($CH_2Cl_2$); UV: 250 (9200; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxalylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethane-sulphonylamino)-acetic acid are reacted in 24 ml of tetrahydrofuran with 0.92 ml of oxalic acid monomethyl ester chloride (16 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 50**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxymalonylaminoethane-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.817 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxy-malonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 6 ml of $CH_2Cl_2$ and 1.92 ml of anisole with 22 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 165° (with decomposition); $[\alpha]_D^{20°}=+94°\pm1°$ (0.75% in $H_2O$); IR: 3700—2600 (broad), 1765, 1665, 1606, 1525 (Nujol); UV: 252 (9800; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxymalonylaminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 4.18 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxy-malonylaminoethanesulphonylamino)-acetic acid are reacted with 2.9 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 25 ml of tetrahydrofuran (0.87 g of hydroxybenzotriazole; three times 0.76 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up, and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+23°\pm1°$ (0.82% in $CHCl_3$); IR: 3400, 3300, 1778, 1710, 1696, 1630, 1520 ($CH_2Cl_2$); UV: 257 (14400; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxymalonylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethane-

sulphonylamino)-acetic acid are reacted in 24 ml of tetrahydrofuran with 1.07 ml of malonic acid monomethyl ester chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 51**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-bromoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.5 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-bromoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 8 ml of $CH_2Cl_2$ and 0.4 ml of anisole with 12 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 220° (with decomposition); IR: *inter alia* 1770 (Nujol); UV: 253 (11100; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-bromoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3.3 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-bromoacetylaminoethanesulphonylamino)-acetic acid are reacted with 2.38 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 25 ml of tetrahydrofuran (0.66 g of hydroxybenzotriazole; three times 0.76 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; IR: 3400, 3300, 1790, 1735, 1682, 1630, 1535 $cm^{-1}$ ($CH_2Cl_2$); UV: 256 (14500; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-bromoacetylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid are reacted in 24 ml of tetrahydrofuran with 0.82 ml of bromoacetyl bromide (16 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 52**

**The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-(1-methyl-1H-tetrazol-5-ylthio)-acetamido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

245 mg of the sodium salt of 1-methyl-1H-mercaptotetrazole are added to 1.5 g of the sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-bromoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid obtainable according to Example 51a) in 30 ml of water and the whole is stirred at room temperature for 3 hours, the pH being maintained constant at 7 by adding 1N sodium hydroxide solution. The mixture is then concentrated *in vacuo*, chromatographed and reprecipitated according to Example 1a). The hydrate of the title compound is obtained; m.p. above 172° (with decomposition); IR: 3700—2700 (broad), 1760, 1650, 1600, 1530 $cm^{-1}$ (Nujol); UV: 252 (8900; $H_2O$).

**Example 53**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxysuccinylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.5 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxysuccinylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 4 ml of $CH_2Cl_2$ and 0.43 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 210° (with decomposition); $[\alpha]_D^{20°} = +89° \pm 1°$ (0.97% in $CHCl_3$); IR: 3650—2700 (broad), 1765, 1730, 1650, 1600, 1525 (Nujol); UV: 252 (9700), 310 (600; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxysuccinylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 4.2 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxysuccinylaminoethanesulphonylamino)-acetic acid are reacted with 3.1 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 45 ml of tetrahydrofuran (1.1 g of hydroxybenzotriazole; three times 0.58 g of dicyclohexyl carbodiimide each time in 6.6 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°} = +16° \pm 1°$ (1.00% in $CHCl_3$); IR: 3400, 3300, 1790, 1730, 1680, 1630, 1543 ($CH_2Cl_2$); UV: 255 (12700; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxysuccinylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethane-

sulphonylamino)-acetic acid are reacted in 25 ml of tetrahydrofuran with 1.22 ml of succinic acid monomethyl ester chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 54**

**a) The disodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-hydroxymalonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.3 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-tert.-butoxymalonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 6.7 ml of $CH_2Cl_2$ and 2.15 ml of anisole with 25 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 200° (with decomposition); $[\alpha]_D^{20°} = \pm 1°$ (0.76% in $H_2O$); IR: 3700—2600 (broad), 1762, 1645, 1595, 1525 (Nujol); UV: 253 (1600), 314 (300; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-tert.-butoxymalonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenyl methyl ester**

Analogously to Example 6b), 6 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester (see Example 35c) for preparation) are reacted with 1.5 g of malonic acid mono-tert.-butyl ester in 25 ml of tetrahydrofuran (0.93 g of hydroxybenzotriazole; three times 0.82 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°} = +25° \pm 1°$ (0.70% in $CHCl_3$); IR: 3400, 1785, 1720, 1675, 1635, 1602, 1535 $cm^{-1}$ ($CH_2Cl_2$); UV: 258 (13700; EtOH).

**Example 55**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzoylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.6 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzoylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 6 ml of $CH_2Cl_2$ and 0.76 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 220° (with decomposition); $[\alpha]_D^{20°} = +79° \pm 1°$ (1.18% in $H_2O$); IR: 3650—2600 (broad), 1765, 1670, 1650, 1598, 1525 (Nujol); UV: 259 (18700; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzoylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzoylamino)-ethanesulphonylamino)-acetic acid are reacted with 3.6 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 60 ml of tetrahydrofuran (1.3 g of hydroxybenzotriazole; three times 0.66 g of dicyclohexyl carbodiimide each time in 6.6 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°} = +14° \pm 1°$ (0.95% in $CHCl_3$); IR: 3400, 3300, 1787, 1725, 1692, 1670, 1650, 1600, 1530 ($CH_2Cl_2$); UV: 259 (23200; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzoylamino)-ethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid are reacted in 25 ml of tetrahydrofuran with 3.7 g of *p*-nitrobenzoyl chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 56**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-acetamidobenzenesulphonylamino)ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as the 2.5-hydrate by reacting 1.4 g (1.5 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-acetamidobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.4 ml of anisole with 7 ml of trifluoroacetic acid in 7 ml of methylene chloride; m.p. above 185° (with decomposition); $R_f$ approximately 0.45 (silica gel Opti-UPC 12, water/acetonitrile 4:1); UV: 256 (28700; water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-acetamidobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a pale yellow, amorphous powder by treating 1.44 g (2.5 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-acetamido-

benzenesulphonylamino)-ethanesulphonylamino)-acetic acid with 0.92 g (2.5 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.34 g of 1-hydroxybenzotriazole and 0.57 g of N,N'-dicyclohexyl carbodiimide in 27 ml of tetrahydrofuran. $R_f$: approxmately 0.10 (silica gel, methylene chloride/ethyl acetate 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-acetamidobenzenesulphonylamino)-ethanesulphonylamino)-acetic acid**

10 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 3.8 g (10 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid. After a reaction period of one hour at 65°, the reaction mixture is cooled to 0°, 0.88 ml of pyridine and 2.65 g of 4-acetamidobenzenesulphonyl chloride are added and the whole is then stirred at room temperature for 20 hours. After removing the solvent, the residue is taken up in 300 ml of ethyl acetate and washed three times with 0.1N hydrochloric acid and three times with saturated, aqueous sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator and the residue is purified over silica gel with ethyl acetate/methanol 4:1 as eluant, to yield the title compound as an amorphous powder. TLC (silica gel): $R_f$: approximately 0.23 (chloroform/methanol/glacial acetic acid 75:22:3).

**Example 57**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-isopropanesulphonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 0.4 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-isopropanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 0.84 ml of $CH_2Cl_2$ and 0.27 ml of anisole with 3.13 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 175° (with decomposition); IR: 3700—2700 (broad), 1762, 1680, 1602, 1520 (Nujol); UV: 250 (9800), 310 (1100; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-isopropanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3.2 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-isopropanesulphonylaminoethanesulphonylamino)-acetic acid are reacted with 2 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 15 ml of tetrahydrofuran (0.6 g of hydroxybenzotriazole; three times 0.52 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained. IR: 3405, 3290, 1781, 1720, 1678, 1520 ($CH_2Cl_2$); UV: 259 (13800; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-isopropanesulphonylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 6c), 8.3 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid are reacted in 30 ml of $CH_2Cl_2$ with 2.66 g of isopropanesulphonyl chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 1.01 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 58**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-ethyl-2,3-dioxopiperazin-1-yl-carbonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as the dihydrate by reacting 2.0 g (2.33 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,4-ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.0 ml of anisole with 10 ml of trifluoroacetic acid in 10 ml of methylene chloride; m.p. above 170° (with decomposition); TLC (silica gel Opti-UPC 12): $R_f$ approximately 0.31 (water/acetonitrile 8:2); $[\alpha]_D^{20°} = +83° \pm 1°$ (1.303% in $H_2O$); UV: 240 (14600; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a yellowish powder by treating 2.20 g (4 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-ethyl-2,3-dioxopiperazin-1-ylcarbonylamino-ethanesulphonylamino)-acetic acid with 1.46 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.54 g of 1-hydroxybenzotriazole and 0.91 g of N,N'-dicyclohexyl carbodiimide in 40 ml of tetrahydrofuran. TLC (silica gel): $R_f$: approximately 0.10 (ethyl acetate).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-ethyl-2,3-dioxopiperazin-1-ylcarbonylamino)-ethanesulphonylamino)-acetic acid**

5 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 3.8 g (10 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid in 50 ml of absolute tetrahydrofuran. After a reaction period of one hour at 65°, the reaction mixture is cooled to room temperature, 2 ml of pyridine and 5.12 g of 4-ethyl-2,3-dioxopiperazin-1-ylcarbonyl chloride are added and the whole is then stirred for 5 hours. After removing the solvent, the residue is taken up in 250 ml of ethyl acetate and washed three times with 1N hydrochloric acid and three times with saturated aqueous sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator, to yield the title compound as an amorphous powder. TLC (silica gel): $R_f$: approximately 0.18 (chloroform/methanol/glacial acetic acid 75:22:3).

**Example 59**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-isopropanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 0.89 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-isopropane-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 2.15 ml of $CH_2Cl_2$ and 0.69 ml of anisole with 8 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. above 220° (with decomposition); $[\alpha]_D^{20°}=+95°\pm1°$ (0.19% in $H_2O$); IR: 3700—2600 (broad), 1760, 1680, 1605, 1522 (Nujol); UV: 250 (10000), 310 (1500; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-isopropanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.99 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-isopropane-sulphonylaminoacetic acid are reacted with 2.4 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 18 ml of tetrahydrofuran (0.72 g of hydroxybenzotriazole; three times 0.62 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+16°\pm1°$ (0.83% in $CHCl_3$); IR: 3400, 3300, 1780, 1715, 1675, 1522 ($CH_2Cl_2$); UV: 258 (14200; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-isopropanesulphonylaminoacetic acid**

Analogously to Example 6c), 3.4 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetic acid are reacted in 30 ml of $CH_2Cl_2$ with 2.66 g of isopropanesulphonyl chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 1.01 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 60**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-n-octylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate by reacting 3.03 g (3.8 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-n-octylsulphonylamino-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 3 ml of anisole with 15 ml of trifluoroacetic acid in 15 ml of methylene chloride; m.p. above 172° (with decomposition); $R_f$ 96: approximately 0.55; $[\alpha]_D^{20°}=+81°\pm1°$ (1.042% in ethaneol/water 1:1); UV: 252 (9100 in ethanol/water 1:1).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-n-octylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as yellowish powder by treating 2.25 g (5 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-n-octylsulphonylaminoacetic acid with 1.83 g (5 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.68 g of 1-hydroxybenzotriazole and 1.14 g of N,N'-dicyclohexyl carbodiimide in 50 ml of tetrahydrofuran. $R_f$: approximately 0.61 (silica gel, methylene chloride/ethyl acetate 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-n-octylsulphonylaminoacetic acid**

8 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 2.73 g (10 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetic acid in 30 ml of absolute tetrahydrofuran. After a reaction period of one hour at 60°, the reaction mixture is cooled to room temperature, 0.8 ml of pyridine and 1.96 ml of 1-octanesulphonyl chloride are added and the whole is then stirred for 16 hours. After removing the solvent, the residue is taken up in 250 ml of ethyl acetate and washed three times with 0.5N

hydrochloric acid and three times with saturated aqueous sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator, and the residue is purified over silica gel with chloroform/ethyl acetate 4:1 as eluant, to yield the title compound as an amorphous powder. $R_f$: approximately 0.58 (silica gel, chloroform/methanol/glacial acetic acid 75:22:3).

**Example 61**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-*p*-toluenesulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.88 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-toluene-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 4.4 ml of $CH_2Cl_2$ and 1.4 ml of anisole with 15 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. above 213° (with decomposition); $[\alpha]_D^{20°}=+96°\pm1°$ (0.91% in $H_2O$); IR: 3650—2700 (broad), 1755, 1657, 1609, 1518 (Nujol); UV: 230 (19000; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-toluenesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.44 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-toluene-sulphonylaminoacetic acid are reacted with 1.8 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 20 ml of tetrahydrofuran (0.52 g of hydroxybenzotriazole; three times 0.46 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran), worked up and chromatographed. 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-toluenesulphonylamino-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester is obtained; $[\alpha]_D^{20°}=+1°\pm1°$ (0.86% in $CHCl_3$); IR: 3400, 3390, 1782, 1720, 1700, 1645, 1600, 1530 ($CH_2Cl_2$); UV: 259 (13000; EtOH).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-toluenesulphonylaminoacetic acid**

Analogously to Example 6c), 2.73 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetic acid are reacted in 24 ml of tetrahydrofuran with 2.1 g of *p*-toluenesulphonyl chloride (10 ml of N,O-bis(trimethylsilyl)acetamide; 0.81 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 62**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-*p*-nitrobenzenesulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the monohydrate by reacting 1.61 g (2.0 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-nitrobenzenesulphonyl-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 3.5 ml of anisole with 8 ml of trifluoroacetic acid in 8 ml of methylene chloride; m.p. above 188° (with decomposition); $R_f$ 96: approximately 0.43; $[\alpha]_D^{20°}=11°\pm1°$ (0.268% in water); UV: 258 (18900; water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-nitrobenzenesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained by treating 2.29 g (5 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-nitrobenzenesulphonylaminoacetic acid with 1.83 g (5 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.68 g of 1-hydroxy-benzotriazole and 1.15 g of N,N'-dicyclohexyl carbodiimide in 30 ml of tetrahydrofuran. $R_f$: approximately 0.83 (methylene chloride/ethyl acetate 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-*p*-nitrobenzenesulphonylaminoacetic acid**

8 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 2.73 g (10 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetic acid in 27 ml of absolute methylene chloride. After a reaction period of one hour at 60°, the reaction mixture is cooled to room temperature, 0.81 ml of pyridine and 2.21 g of *p*-nitrobenzenesulphonyl chloride are added and the whole is then stirred for 5 hours. After removing the solvent, the residue is taken up in 250 ml of ethyl acetate and washed three times with 1.0N hydrochloric acid and three times with saturated aqueous sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator and the residue is purified over silica gel with methylene chloride/ethyl acetate 1:1 as eluant, to yield the title compound as an amorphous powder. $R_f$ 96: approximately 0.65.

**Example 63**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(4-acetamidobenzenesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate by

reacting 4.0 g (4.9 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(4-acetamidobenzene-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 4 ml of anisole with 20 ml of trifluoroacetic acid in 20 ml of methylene chloride; m.p. above 191° (with decomposition); $R_f$: approximately 0.33 (silica gel Opti-UPC 12, water/acetonitrile 9:1); $[\alpha]_D^{20°}$=+91°±1° (0.982% in water); UV: 260 (27200; water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(4-acetamidobenzenesulfonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a beige powder by treating 2.35 g (5 mmol) of (2R,S)-2-(2-BOC-aminothiazole-4-yl)-2-(4-acetamidobenzenesulphonylamino)-acetic acid with 1.83 g (5 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.675 g of 1-hydroxybenzotriazole and 1.15 g of N,N'-dicyclohexyl carbodiimide in 25 ml of tetrahydrofuran. $R_f$: approximately 0.40 (silica gel, ethyl acetate).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(4-acetamidobenzenesulphonylamino)-acetic acid**

8 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 2.73 g (10 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetic acid in 30 ml of absolute tetrahydrofuran. After a reaction period of one hour at 60°, the reaction mixture is cooled to room temperature, 0.8 ml of pyridine and 2.34 g of 4-acetamino-benzenesulphonyl chloride are added and the whole is then stirred for 4 hours. After removing the solvent, the residue is taken up in 250 ml of ethyl acetate and washed three times with 1N hydrochloric acid and three times with saturated aqueous sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator and the title compound is obtained as an amorphous powder. $R_f$ 96: approximately 0.68.

**Example 64**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminonaphth-1-ylsulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.57 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminonaphth-1-yl-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 3.4 ml of $CH_2Cl_2$ and 1.07 ml of anisole with 12.5 ml of trifluoroacetic acid, worked up and reprecipitated. The hydrate of the title compound is obtained; m.p. above 215° (with decomposition); $[\alpha]_D^{20°}$=+90°±1° (0.078% in $H_2O$); IR: 3650—2700 (broad), 1762, 1680, 1628, 1605, 1555, 1520 (Nujol); UV: 243 (44800), 347 (3900; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminonaphth-1-ylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 37c), 2.71 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-naphth-1-ylsulphonylamino)acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted with 2.4 g of zinc dust in 30 ml of acetonitrile/glacial acetic acid 1:1 mixture and worked up. After purifying the crude product by chromatography over 100 g of silica gel (eluant: toluene/ethyl acetate 1:1 mixture), the title compound is obtained; $[\alpha]_D^{20°}$=−5°±1° (0.70% in $CHCl_3$); IR: 3500, 3395, 3300, 1785, 1720, 1700, 1628, 1600, 1535, 1508 ($CH_2Cl_2$); UV: 245 (57800), 350 (4300; EtOH).

**c) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-naphth-1-ylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

7.41 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 7.41 g of 2-(2,2,2-trichloroethoxycarbonylamino)-naphth-1-ylsulphonyl chloride are stirred for 6 hours at room temperature in 75 ml of tetrahydrofuran and 0.963 ml of pyridine. The reaction mixture is then taken up in ethyl acetate, washed with 1N hydrochloric acid and saturated aqueous sodium chloride solution, dried over $Na_2SO_4$ and concentrated by evaporation. After purifying the crude product by chromatography over 250 g of silica gel (eluant: toluene/ethyl acetate 9:1 mixture), the title compound is obtained; $[\alpha]_D^{20°}$=−5°±1° (1.00% in $CHCl_3$); IR: 3400, 3300, 1785, 1750, 1724, 1700, 1620, 1605 ($CH_2Cl_2$); UV: 249 (58800), 325 (4400; EtOH).

Preparation of the starting material:

**d) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 7c), 7.52 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-chloroacetyl-aminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester (see Example 7d) for preparation) are reacted with 1.76 g of thiourea (125 ml of dioxan; 2.58 ml of acetic acid) and worked up. The title compound is obtained and is further processed in the crude state without being characterised.

**Example 65**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(5-imidazolesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.6 g of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(5-imidazole-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 10 ml of $CH_2Cl_2$ and 0.56 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 230° (with decomposition); $[\alpha]_D^{20°}=+83°\pm1°$ (1.01% in $H_2O$); IR: 3700—2600 (broad), 1760 (broad), 1680, 1640, 1600, 1520 (Nujol); UV: 250 (9200; $H_2O$).

**b) 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(5-imidazolesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 64c), 2.9 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-amino-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester (see Example 64d) for preparation) and 0.8 g of 5-imidazolesulphonyl chloride are reacted in 30 ml of tetrahydrofuran and 0.55 ml of N-methylmorpholine, worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=-6°\pm1°$ (0.077% in $CHCl_3$); IR: 3450—2700 (broad), 1785, 1725, 1700 (shoulder), 1640 (shoulder), 1602, 1545 ($CH_2Cl_2$). UV: 258 (14100; EtOH).

**Example 66**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the dihydrate of the title compound is obtained by reacting 3.7 g (3.6 mmol) of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 3.7 ml of anisole with 18.5 ml of trifluoroacetic acid in 18.5 ml of methylene chloride; m.p. above 160° (with decomposition); $R_f$: approximately 0.10 (silica gel Opti-UPC 12, water/acetonitrile 4:1); $[\alpha]_D^{20°}=22°\pm1°$ (0.595% in water); UV: 259 (25000 in water).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a yellowish powder by treating 3.1 g (5.5 mmol) of (2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethane-sulphonylamino)-acetic acid with 2.72 g (5.5 mmol) of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1-hydroxybenzotriazole and 1.25 g of N,N'-dicyclohexyl carbodiimide in 50 ml of tetrahydrofuran. $R_f$: approximately 0.43 (silica gel, methylene chloride/ethyl acetate 1:1).

**Example 67**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as a pale yellowish powder in the form of the dihydrate by reacting 1.58 g (1.6 mmol) of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.7 ml of anisole with 8 ml of trifluoroacetic acid in 8 ml of methylene chloride; m.p. above 112° (with decomposition); $R_f$: approximately 0.18 (silica gel Opti-UPC 12, water/acetonitrile 4:1); $[\alpha]_D^{20°}=+45°\pm1°$ (0.766% in water); UV: 256 (23700 in water).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzene-sulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a pale yellow amorphous powder by treating 4.52 g (8.0 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonyl-amino)-ethanesulphonylamino)-acetic acid with 3.51 g (8 mmol) of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.08 g of 1-hydroxybenzotriazole and 1.81 g of N,N'-dicyclohexyl carbodiimide in 80 ml of tetrahydrofuran. $R_f$: approximately 0.33 (silica gel, methylene chloride/ethyl acetate 1:1).

**Example 68**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonyl-amino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as a yellowish powder in the form

of the trihydrate by reacting 1.77 g (2 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.8 ml of anisole with 9 ml of trifluoroacetic acid in 9 ml of methylene chloride; m.p. above 170° (with decomposition); $[\alpha]_D^{20°}$=+72°±1° (0.743% in water); UV: 257 (24200 in water).

Preparation of the starting material:

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 1.83 g (2 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester is hydrogenated at room temperature under normal pressure in the presence of 0.85 g of 10% palladium-on-carbon catalyst. Residual solid material is filtered off, washed with ethyl acetate, the filtrate is concentrated and the title compound is obtained as a yellowish powder. $R_f$: approximately 0.31 (silica gel, methylene chloride/ethyl acetate 1:1).

**Example 69**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.9 g of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 8.9 ml of $CH_2Cl_2$ and 2.97 ml of anisole with 33.4 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 160° (with decomposition); $[\alpha]_D^{20°}$=+62°±1° (1.20% in $H_2O$); IR: 3650—2500 (broad), 1760, 1695, 1605, 1520 $cm^{-1}$; UV: 255 (12500 in $H_2O$).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.5 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetic acid (see Example 22c) for preparation) are reacted with 2.59 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 33 ml of tetrahydrofuran (0.63 g of hydroxybenzotriazole; three times 0.58 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}$=−9°±1° (0.97% in $CHCl_3$); IR: 3500, 3400, 3270, 1770, 1700, 1680 (shoulder), 1560, 1515 $cm^{-1}$ ($CH_2Cl_2$); UV: 257 (16200; EtOH).

**Example 70**

**a) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

1.65 g of the sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (see Example 22a) for preparation) and 0.735 ml of iodomethyl pivalate are stirred in 16.5 ml of dimethylformamide at 0° for 30 minutes. 10 ml of phosphate buffer of pH 8 are then added and the mixture is stirred again at 0° for 5 minutes. The mixture is then taken up in 25 ml of ethyl acetate, washed twice with saturated aqueous NaCl solution and dried over sodium sulphate. Filtration is then carried out and 4.5 ml of 0.7N HCl in $CH_2Cl_2$ are added. The amorphous precipitate which forms is decanted off, washed three times with hexane and dried at room temperature *in vacuo*. The material is then digested with ether, filtered off from the ether and again dried. The title compound is obtained; m.p. above 110° (with decomposition); $[\alpha]_D^{20°}$=−21°±1° (1.07% in DMSO); IR: 3600—2400 (broad), 1782, 1750, 1695, 1628, 1545 $cm^{-1}$ (Nujol); UV: 258 (12000; $CH_3OH$).

**Example 71**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.5 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 5 ml of $CH_2Cl_2$ and 0.7 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 210° (with decomposition); $[\alpha]_D^{20°}$=−9°±1° (0.91% in $H_2O$); IR: 3650—2500 (broad), 2260, 1760, 1685, 1605, 1520 (Nujol); UV: 257 (13600; $H_2O$).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.6 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetic acid (see Example 44c) for preparation) are reacted with 3.3 g of 3-(1-methyl-

1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 30 ml of tetrahydrofuran (0.9 g of hydroxybenzotriazole; three times 0.43 g of dicyclohexyl carbodiimide each time in 6.6. ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}$=—85°±1° (0.97% in $CHCl_3$); IR: 3400, 3300, 2260, 1785, 1722, 1700 (shoulder), 1625, 1540 ($CH_2Cl_2$); UV: 258 (15800; EtOH).

**Example 72**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.2 g of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 4 ml of $CH_2Cl_2$ and 0.636 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 190° (with decomposition); $[\alpha]_D^{20°}$=+53°±1° (1.03% in $H_2O$); IR: 3650—2500 (broad), 1760, 1670, 1605, 1520 $cm^{-1}$ (Nujol); UV: 257 (13300; $H_2O$).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.3 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetic acid (see Example 27c) for preparation) are reacted with 2.4 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 30 ml of tetrahydrofuran (0.5 g of hydroxybenzotriazole; three times 1.2 g of dicyclohexyl carbodiimide each time in 10 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}$=+1°±1° (1.01% in $CHCl_3$); IR: *inter alia* 1785 $cm^{-1}$ ($CH_2Cl_2$); UV: 258 (14400; EtOH).

**Example 73**

**a) The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.7 g of 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 14 ml of $CH_2Cl_2$ and 0.73 ml of anisole with 21 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 165° (with decomposition); $[\alpha]_D^{20°}$=+77°±1° (0.85% in $H_2O$); IR: 3650—2500 (broad), 1760, 1725 (shoulder), 1670, 1605, 1520 (Nujol); UV: 256 (12000; $H_2O$).

**b) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.3 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetic acid (see Example 27c) for preparation) are reacted with 2.1 g of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 30 ml of tetrahydrofuran (0.5 g of hydroxybenzotriazole; three times 0.4 g of dicyclohexyl carbodiimide each time in 6 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}$=+56°±1° (1.28% in $CHCl_3$); IR: 3300, 1780, 1720, 1680, 1550 (Nujol); UV: 257 (15600; EtOH).

**Example 74**

**7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70, 1 g of the sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid and 0.5 ml of iodomethyl pivalate are reacted in 10 ml of dimethylformamide and worked up. The title compound is obtained; $[\alpha]_D^{20°}$=+63°±1° (0.95% in DMSO); IR: 3650—2400 (broad), 1780, 1750, 1670 (broad), 1630, 1540 (Nujol); UV: 258 (11500; $CH_3OH$).

**Example 75**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.65 g of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 4.9 ml of $CH_2Cl_2$ and 1.6 ml of anisole with 18 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 170° (with decomposition); $[\alpha]_D^{20°}$=+83°±1° (0.95% in $H_2O$); IR: 3650—2500 (broad), 1760, 1695, 1605, 1520 (Nujol); UV: 255 (12600; $H_2O$).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.65 g of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 4.9 ml of $CH_2Cl_2$ and 1.6 ml of anisole with 18 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 175° (with decomposition); $[\alpha]_D^{20°}=+48°\pm1°$ (0.96% in $H_2O$); IR: 3650—2500 (broad), 1760, 1695, 1605, 1520 (Nujol); UV: 255 (12400; $H_2O$).

**c) 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.5 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methanesulphonylaminoacetic acid (see Example 22c) for preparation) are reacted with 2.59 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 33 ml of tetrahydrofuran (0.63 g of hydroxybenzotriazole; three times 0.58 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran) and worked up. The resulting crude product is chromatographed over 300 g of silica gel (graduated column) [eluant: toluene/ethyl acetate 2:1 and 1:1 mixture]. In so doing, the title compound having the 2R-configuration is eluted first (see Example 7d) for assignment of configuration); $[\alpha]_D^{20°}=-5°\pm1°$ (1.08% in $CHCl_3$); IR: 3520, 3410, 3280, 1795, 1725, 1700 (shoulder), 1582, 1540 ($CH_2Cl_2$); UV: 259 (15200 in $C_2H_5OH$).

Higher fractions consist of a binary mixture of the above (2R)-compound with the (2S)-isomer.

The title compound having the 2S-configuration is obtained from the last fractions. $[\alpha]_D^{20°}=-7°\pm1°$ (0.99% in $CHCl_3$); IR: 3520, 3410, 3290, 1780, 1725, 1695 (shoulder), 1582, 1540 ($CH_2Cl_2$); UV: 258 (16400; EtOH).

**Example 76**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

4 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are dissolved in 7 ml of methylene chloride. 1.5 ml of anisole and 70 ml of trifluoroacetic acid are added in succession to the solution and the whole is stirred at room temperature for one hour with the exclusion of moisture. A voluminous precipitate forms in the initially clear solution. The suspension is then poured into an ice-cold mixture of 600 ml of petroleum ether and 300 ml of diethyl ether, the resulting trifluoroacetate is filtered off with suction, washed with petroleum ether and dried at room temperature under a high vacuum. The crude trifluoroacetate salt is then dissolved in 30 ml of acetonitrile/water mixture, the solution is cooled to +5° and, while stirring and cooling, adjusted to a pH value of 5.8 by adding dropwise 1N sodium hydroxide solution. The solution is then poured into 600 ml of ethanol and concentrated to a volume of approximately 100 ml at 50° in a rotary evaporator. This operation is repeated twice with 300 ml of ethanol being added each time, the amorphous product being precipitated. The precipitate is filtered off with suction and washed in succession with ethanol, a mixture of ethanol/diethyl ether and diethyl ether. The hydrate of the title compound is obtained. Melting point from 146° with decomposition; $[\alpha]_D^{20°}=-7°\pm1°$ (2.039% in 0.1N $NaHCO_3$). IR: 3310 (broad), 3200, 1785 (shoulder), 1765 (broad), 1685, 1610 (broad), 1525, 1375, 1350, 1175, 1145 (in Nujol). $R_f$: approximately 0.44 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 42c), the title compound is obtained by reacting 3.0 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-acetic acid (see Example 43d) for preparation) with 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.50 g of 1-hydroxybenzotriazole and 1.60 g (2×0.80 g) of N,N′-dicyclohexyl carbodiimide in 50 ml of a mixture of dioxan/tetrahydrofuran (1:1). The crude product is purified over 20 times the amount of silica gel. Eluant: methylene chloride with from 10 to 20% of methyl acetate. $R_f$: approximately 0.52 (silica gel, UV 336, double spot diastereoisomeric mixture, chloroform/ethyl acetate/ethanol 42.5:42.5:5).

**Example 77**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 3.4 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 60 ml of trifluoroacetic acid in 5 ml of methylene

chloride and 1.2 ml of anisole and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. The amorphous product melts above 178° with decomposition. $[\alpha]_D^{20°}=+83°\pm1°$ (2.039% in 0.1N $NaHCO_3$). IR: 3320 (broad), 3190 (broad), 1760 (broad), 1645, 1600, 1565, 1520, 1375, 1365, 1165, (shoulder), 1140 (in Nujol); $R_f$: 0.33 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 42c), the title compound is obtained by reacting 3.0 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetic acid with 2.50 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.60 g (2×0.80 g) of N,N'-dicyclohexyl carbodiimide in 50 ml of tetrahydrofuran. The crude product is purified over 25 times the amount of silica gel. Eluant: methylene chloride/methyl acetate (1:1). M.p. above 140° (with decomposition); $R_f$: 0.15 (silica gel, UV 366, double spot diastereoisomeric mixture, chloroform/ethyl acetate/ethanol 42.5:42.5:5).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetic acid**

18 ml of 1N sodium hydroxide solution are added to a solution of 3.8 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetic acid methyl ester in 15 ml of methanol and 10 ml of water and the reaction mixture is stirred at 30° for 4 hours. The resulting acid is then isolated analogously to Example 43d). After evaporating off the solvent, the title compound remains behind as a foam. M.p. 93—96° (with decomposition).

**d) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetic acid methyl ester**

A solution of 0.80 g of methyl isocyanate in 8 ml of tetrahydrofuran is added dropwise at 2° while stirring for 30 minutes to a solution of 4.70 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid methyl ester in 40 ml of tetrahydrofuran. The reaction mixture is then stirred for 4 hours at +2° and for one hour at room temperature. The solution is then concentrated to dryness at 50° in a rotary evaporator and the crude product is purified over 20 times the amount of silica gel. Eluant: methylene chloride with from 55 to 70% of methyl acetate. The title compound is obtained as a foam; m.p. above 70° (with decomposition). $R_f$: approximately 0.07 (silica gel, UV 336, toluene/chloroform/ethyl acetate 1:1:1).

**Example 78**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-anilinoformamidoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 2.70 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-anilinoformamidoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 50 ml of trifluoroacetic acid in 1.0 ml of anisole and 5 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. The amorphous product melts above 210° with decomposition. IR: 3360, 3305, 3270, 3180 (broad), 1785 (shoulder), 1760, 1650, 1640, 1590, 1560, 1535, 1510, 1375, 1365, 1145, 113 (in Nujol); $R_f$ 96: approximately 0.29.

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-anilinoformamidoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 42c), the title compound is obtained by reacting 2.8 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-anilinoformamidoethanesulphonylamino)-acetic acid with 2.10 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.20 g (2×0.60 g) of N,N'-dicyclohexyl carbodiimide in 50 ml of tetrahydrofuran. The crude product is purified over 20 times the amount of silica gel. Eluant: methylene chloride with from 15 to 25% of methyl acetate. M.p. above 128—131° with decomposition. $R_f$: approximately 0.43 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/chloroform/ethyl acetate 1:1:1+5% ethanol).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-anilinoformamidoethanesulphonylamino)-acetic acid**

Analogously to Example 43d), the title compound is obtained by reacting 2.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-anilinoformamidoethanesulphonylamino)-acetic acid methyl ester in 25 ml of methanol with 6 ml of 2N sodium hydroxide solution and stirring for 4 hours at 40°. $R_f$ 96: approximately 0.69.

**d) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-anilinoformamidoethanesulphonylamino)-acetic acid methyl ester**

Analogously to Example 77d), a solution of 4.54 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetic acid methyl ester in 30 ml of tetrahydrofuran is reacted with 1.60 ml of phenyl isocyanate in 20 ml of tetrahydrofuran, the reaction mixture is evaporated to dryness at 50° in a rotary evaporator and the crude product is purified over 15 times the amount of silica gel. Eluant: methylene chloride with from 15 to 25% of methyl acetate. The title compound is obtained as a foam. $R_f$ 0.24 (silica gel, UV 366, toluene/chloroform/ethyl acetate 1:1:1+3% ethanol).

**Example 79**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 43a), the title compound is obtained by reacting 3.6 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 45 ml of trifluoroacetic acid in 2.10 ml of anisole and 5 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. above 160° with decomposition; $[\alpha]_D^{20°}=-34°\pm1°$ (2.207% in dimethyl sulphoxide); $R_f$: 0.35 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 42c), the title compound is obtained by reacting 2.20 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-methylaminoethanesulphonylamino)-acetic acid with 1.8 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.27 g of 1-hydroxybenzotriazole and 0.90 g (2×0.45 g) of N,N'-dicyclohexyl carbodiimide in 45 ml of tetrahydrofuran. The crude product is purified over 40 times the amount of silica gel. Eluant: methylene chloride/methyl acetate (85:15). $R_f$: approximately 0.48 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/ethyl acetate 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-methylaminoethanesulphonylamino)-acetic acid**

9.5 g of (2R,S)-2-[2-(N-methyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino]-2-(2-BOC-aminothiazol-4-yl)-acetic acid (preparation Example 42d)) are treated in 100 ml of acetonitrile/glacial acetic acid 1:1 with 12.0 g (9.5 g+2.5 g) of zinc dust. Working up analogously to Example 13d). A solution of the crude product is poured into n-hexane, with the amorphous (2R,S)-2-(2-N-methylaminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid being precipitated. $R_f$: approximately 0.13 (silica gel, UV 366, chloroform/methanol/glacial acetic acid/water 45:12:1:2). 45 g of this acid are reacted analogously to Example 13c) in 60 ml of dioxan and 30 ml of water with 6.4 ml of di-tert.-butyl dicarbonate in the presence of 4.3 g of sodium carbonate. After mixing the crude product with petroleum ether, the amorphous title compound is obtained. $R_f$: approximately 0.58 (silica gel, UV 366, chloroform/methanol/glacial acetic acid/water 45:12:1:2).

**Example 80**

**a) 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-n-butylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-n-butylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 50 ml of trifluoroacetic acid in 1.0 ml of anisole and 5 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. The amorphous product melts at 166—173° with decomposition. IR: 3310 (broad), 3190, 1785 (shoulder), 1765 (broad), 1680, 1600 (broad), 1520, 1355 (broad), 1175 (shoulder), 1150 (in Nujol); $R_f$: approximately 0.38 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-n-butylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 43c), the title compound is obtained by reacting (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-n-butylaminoethanesulphonylamino)-acetic acid with 1.5 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.98 g (2×0.49 g) of dicyclohexyl carbodiimide in 50 ml of tetrahydrofuran. The crude product is purified over 25 times the amount of silica gel. Eluant: methylene chloride with from 7 to 10% of methyl acetate. $R_f$: approximately 0.45 (silica gel, UV 366, toluene/ethyl acetate 2:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-n-butylaminoethanesulphonylamino)-acetic acid**

7.1 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(n-butyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-acetic acid are treated in 80 ml of glacial acetic acid/acetonitrile (1:1) with 14.0 g (10.0 g and 4.0 g) of zinc dust. The reaction mixture is worked up analogously to Example 13d). On mixing the crude product with diethyl ether, amorphous (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-n-butylaminoethanesulphonylaminoacetic acid is obtained. $R_f$ 96: approximately 0.42 (silica gel, UV 366). 8.9 g of this acid are dissolved in 80 ml of dioxan and reacted analogously to Example 13c) in 20 ml of water with 4.7 ml of di-tert.-butyl dicarbonate in the presence of 2.5 g of sodium carbonate. The crude product is purified over 20 times the amount of silica gel. Eluant: methylene chloride with from 10 to 30% of methyl acetate. The title compound is obtained. $R_f$ 96: 0.45 (silica gel, UV 366).

**d) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(n-butyl-2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-acetic acid**

The trimethylsilyl ester of 10 g of (2R,S)-2-amino-2-(2-BOC-aminothiazol-4-yl)-acetic acid is reacted analogously to Example 42d) with 20 g of oily 2-(N-n-butyl-2,2,2-trichloroethoxycarbonyl-amino)ethanesulphonyl chloride (prepared according to Example 42e)). The crude product is purified over 20 times the amount of silica gel. Eluant: methylene chloride with from 10 to 30% of methyl acetate. The title compound is obtained. $R_f$ 96: 0.64 (silica gel, UV 366).

**Example 81**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethy)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.5 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 81b) are reacted in 6 ml of $CH_2Cl_2$ and 0.9 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. decomposition above 205°; $[\alpha]_D^{20°}=-2°\pm1°$ (0.93% in $H_2O$); IR: 3650—2500 (broad), 1763, 1665, 1600, 1520 (Nujol); UV: 258 (12600; $H_2O$).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 5.5 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetyl-aminoethanesulphonylamino)-acetic acid obtainable according to Example 36c) are reacted with 6.0 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 55 ml of tetrahydrofuran (1.6 g of hydroxybenzotriazole; three times 0.83 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=-73°\pm1°$ (0.88% in $CHCl_3$); IR: 3400, 3180 (broad), 1787, 1720, 1683, 1538 ($CH_2Cl_2$); UV: 260 (16800; EtOH).

**Example 82**

**3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxy-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 0.5 g of the sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (see Example 81a) for preparation) and 0.19 ml of iodomethyl pivalate are reacted in 5 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 150° (with decomposition); $[\alpha]_D^{20°}=-18°\pm1°$ (1.03% in DMSO); IR: 3660—2300 (broad), 17 1748, 1690 (shoulder), 1660—1620 (broad), 1540 (Nujol); UV: 260 (12000; $CH_3OH$).

**Example 83**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 6 g of the 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 83b) are reacted in 10 ml of $CH_2Cl_2$ and 1.5 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 205° (with decomposition); $[\alpha]_D^{20°}=+25°\pm1°$ (1.02% in $H_2O$); IR: 3660—2500 (broad), 1760, 1680 (shoulder), 1630 (shoulder), 1600, 1578, 1522 (Nujol); UV: 230 (20000), 260 (shoulder; $H_2O$).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 8 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetic acid obtainable according to Example 26c) are reacted with 7.4 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 80 ml of tetrahydrofuran (2.0 g of hydroxybenzotriazole; three times 1 g of dicyclohexyl carbodiimide each time in 8.3 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=-67°\pm1°$ (1.00% in $CHCl_3$); IR: 3400, 3300 (broad), 1788, 1722, 1698 (shoulder), 1663, 1601, 1579, 1538 ($CH_2Cl_2$); UV: 259 (15800; $CH_2Cl_2$).

**Example 84**

**3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 0.8 g of the sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-benzoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (see Example 83a) for preparation) and 0.3 ml of iodomethyl pivalate are reacted in 8 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 195° (with decomposition); $[\alpha]_D^{20°}=-12°\pm1°$ (0.69% in DMSO); IR: 3660—2500 (broad), 1782, 1750, 1692, 1630, 1600 (shoulder), 1577, 1535 (Nujol); UV: 220 (21000), 258 (13700; $CH_3OH$).

**Example 85**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.13 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 85b) are reacted in 4.1 ml of $CH_2Cl_2$ and 1.35 ml of anisole with 15.5 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 157° (with decomposition); $[\alpha]_D^{20°}=0°$ (0.75% in $H_2O$); IR: 3660—2500, 1763, 1690 (shoulder), 1660, 1625 (shoulder), 1600, 1550 (shoulder), 1525 (Nujol); UV: 255 (13500; $H_2O$).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 2.88 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetic acid obtainable according to Example 31c) are reacted with 2.9 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 30 ml of tetrahydrofuran, (0.66 g of hydroxybenzotriazole; three times 0.58 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=-66°\pm1°$ (0.98% in $CHCl_3$); IR: 3390, 3290, 1775, 1710, 1690 (shoulder), 1670 (shoulder), 1620, 1600 (shoulder), 1515 ($CH_2Cl_2$); UV: 260 (16000; EtOH).

**Example 86**

**3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 1.815 g of the sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (see Example 69a) for preparation) and 0.9 ml of iodomethyl pivalate are reacted in 18.15 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 123° (with decomposition); $[\alpha]_D^{20°}=+30°\pm1°$ (0.81% in DMSO); IR: 3660—2300 (broad), 1780, 1745, 1700, 1630, 1545 (Nujol); UV: 260 (11800; $CH_3OH$).

**Example 87**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.62 g of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 87c) are reacted in 5.4 ml of $CH_2Cl_2$ and 1.76 ml of anisole with 20 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 155° (with decomposition); $[\alpha]_D^{20°}=+40°\pm1°$ (0.85% in $H_2O$); IR: 3660—2500 (broad), 1760, 1700, 1658, 1605, 1522 (Nujol); UV: 253 (12800; $H_2O$).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.45 g of the 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 87c) are reacted in 7 ml of $CH_2Cl_2$ and 2.3 ml of anisole with 26 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 160° (with decomposition); $[\alpha]_D^{20°}=+69°\pm1°$ (0.92% in $H_2O$); IR: 3660—2500 (broad), 1762, 1700 (shoulder), 1600, 1605, 1522 (Nujol); UV: 253 (13800; $H_2O$).

**c) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 9.93 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetic acid obtainable according to Example 31c) are reacted with 8.95 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 70 ml of tetrahydrofuran (2.28 g of hydroxybenzotriazole; three times 2.0 g of dicyclohexyl carbodiimide each time in 10 ml of tetrahydrofuran) and worked up. The resulting crude product is chromatographed over 700 g of silica gel [eluant: toluene/ethyl acetate 7:3, 3:2, 1:1 and 1:2 mixtures]. In so doing, the title compound having the 2R-configuration is eluted first (see Example 7d) for assignment of configuration); $[\alpha]_D^{20°}=-5°\pm1°$ (0.75% in $CHCl_3$); IR: 3520, 3420, 3300, 3200 (shoulder), 1775, 1712, 1670 (shoulder), 1620, 1580, 1520, ($CH_2Cl_2$); UV: 259 (16000; EtOH).

The next fractions consist of a binary mixture of the above (2R)-compound with the (2S)-isomer.

The title compound having the (2S)-configuration is obtained for the last fractions; $[\alpha]_D^{20°}=+4°\pm1°$ (0.91% in $CHCl_3$); IR: 3550, 3429, 3300, 3200 (shoulder), 1778, 1715, 1700 (shoulder), 1670 (shoulder), 1620 (shoulder), 1600, 1580, 1522 ($CH_2Cl_2$); UV: 259 (16200; EtOH).

**Example 88**

**3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 0.54 g of the sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (see Example 87a) for preparation) and 0.23 ml of iodomethyl pivalate are reacted in 5.4 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 130° (with decomposition); IR: 3660—2400 (broad), 1780, 1748, 1700, 1660, 1627, 1545 (Nujol); UV: 259 (11000; $CH_3OH$).

**Example 89**

**3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 0.67 g of the sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (see Example 87b) for preparation) and 0.29 ml of iodomethyl pivalate are reacted in 6.7 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 125° (with decompodition); IR: 3660—2400 (broad), 1780, 1748, 1700, 1660, 1627, 1545 (Nujol); UV: 259 (11000; $CH_3OH$).

**Example 90**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.5 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 90b) are reacted in 6 ml of $CH_2Cl_2$ and 0.9 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 180° (with decomposition); $[\alpha]_D^{20°}=-2°\pm1°$ (0.81% in $H_2O$); IR: 3660—2500 (broad), 1765, 1690—1600 (broad), 1522 (Nujol); UV: 260 (13200; $H_2O$).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 4.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetic acid obtainable according to Example 24c) are reacted with 4.5 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in

50 ml of tetrahydrofuran (1.2 g of hydroxybenzotriazole; three times 0.6 g of dicyclohexyl carbodiimide each time in 5 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=-76°\pm1°$ (1.47% in $CHCl_3$); IR: 3420 (shoulder), 3398, 3300 (broad), 1789, 1722, 1676, 1543 ($CH_2Cl_2$); UV: 260 (16600; EtOH).

**Example 91**

**3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 0.5 g of the sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (see Example 90a) for preparation) and 0.2 ml of iodomethyl pivalate are reacted in 5 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 180° (with decomposition); $[\alpha]_D^{20°}=-20°\pm1°$ (1.08% in DMSO); IR: 3660—2500 (broad), 1785, 1750, 1694, 1630, 1545 (Nujol); UV: 260 (12800; $CH_3OH$).

**Example 92**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.1 g of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 92c) are reacted in 5 ml of $CH_2Cl_2$ and 0.3 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 190° (with decomposition); $[\alpha]_D^{20°}=+49°\pm1°$ (0.84% in $H_2O$); IR: 3660—2500 (broad), 1762, 1670, 1610, 1525 (Nujol); UV: 255 (12200; $H_2O$).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.7 g of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 92c) are reacted in 5 ml of $CH_2Cl_2$ and 0.47 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 190° (with decomposition); $[\alpha]_D^{20°}=+6°\pm1°$ (0.99% in $H_2O$); IR: 3660—2500 (broad), 1762, 1705 (shoulder), 1670, 1605, 1525 (Nujol); UV: 255 (12800; $H_2O$).

**c) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 6.7 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxycarbonylaminoethanesulphonylamino)-acetic acid obtainable according to Example 36c) are reacted with 6 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 70 ml of tetrahydrofuran (1.8 g of hydroxybenzotriazole; three times 0.93 g of dicyclohexyl carbodiimide each time in 6.6 ml of tetrahydrofuran), and worked up. The resulting crude product is chromatographed over 400 g of silica gel [eluant: toluene/ethyl acetate 4:1, 1:1 and 1:2 mixtures and ethyl acetate]. In so doing, the title compound having the 2R-configuration is eluted first (see Example 7d) for assignment of configuration); $[\alpha]_D^{20°}=-20°\pm1°$ (0.25% in $CHCl_3$); IR: 3530, 3415, 3280 (broad), 1787, 1728, 1690, 1583, 1542 ($CH_2Cl_2$); UV: 259 (16600; EtOH).

The next fractions consist of a binary mixture of the above (2R)-compound with the (2S)-isomer.

The title compound having the 2S-configuration is obtained from the last fractions; $[\alpha]_D^{20°}=+7°\pm1°$ (0.92% in $CHCl_3$); IR: 3525, 3418, 3290 (broad), 1785, 1728, 1685, 1584, 1542 ($CH_2Cl_2$); UV: 259 (16000; EtOH).

**Example 93**

**a) The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 10.0 g of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 93b) are reacted in 15 ml of $CH_2Cl_2$ and 2.82 ml of anisole with 20 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 180° (with decomposition); $[\alpha]_D^{20°}=+155°\pm1°$ (1.08% in $H_2O$); IR: 3660—2500 (broad), 2110, 1758, 1680 (shoulder), 1650—1610 (broad), 1520 (Nujol); UV: 250 (16000; $H_2O$).

**b) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 15 g of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 83c) are reacted with 1.15 ml of propiolic acid in 200 ml of tetrahydrofuran (2.5 g of hydroxybenzotriazole; three times 1.3 g of dicyclohexyl carbodiimide each time in 20 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; IR: 3400, 3300, 2120, 1790, 1726, 1700 (shoulder), 1668, 1603, 1540, ($CH_2Cl_2$); UV: 258 (13500; EtOH).

Preparation of the starting material:

**c) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 35c), 5.5 g of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 83d) are reacted with 5.5 g of zinc dust in 60 ml of acetonitrile/acetic acid 1:1 mixture and worked up. The title compound is obtained; $[\alpha]_D^{20°}=+67°\pm1°$ (0.78% in $CHCl_3$); IR: 3320 (shoulder), 3270, 1785, 1740 (shoulder), 1725, 1680 (shoulder), 1626, 1550 (Nujol); UV: 257 (12400; EtOH).

**d) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 4.6 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,2,2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-acetic acid obtainable according to Example 13e) are reacted with 3.29 g of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 40 ml of tetrahydrofuran (0.76 g of hydroxybenzotriazole; three times 0.67 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=0°$ (0.79% in $CHCl_3$); IR: 3420 (shoulder), 3400, 3290, 1787, 1740 (shoulder), 1730, 1700 (shoulder), 1605 (weak), 1541, 1525 (shoulder), 1498 (Nujol); UV: 257 (15300; EtOH).

**Example 94**

**7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 1.78 g of the sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (see Example 2a) for preparation) and 1.027 ml of iodomethyl pivalate are reacted in 17.8 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 140° (with decomposition); $[\alpha]_D^{20°}=+70°\pm1°$ (0.88% in DMSO); IR: 3660—2300 (broad), 1780, 1750, 1695, 1630, 1540 (Nujol); UV: 256 (11000; $CH_3OH$).

**Example 95**

**The disodium salt of 3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 18, the hydrate of the title compound is obtained starting from 1.26 g of the sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (see Example 1a) for preparation) and 1.33 g of the sodium salt of 1-sulphomethyl-5-mercapto-1H-tetrazole in 4.2 ml of water; m.p. above 180° (with decomposition); $[\alpha]_D^{20°}=+9°\pm1°$ (0.77% in $H_2O$); IR: 3660—2500 (broad), 1760, 1682, 1605, 1550 (shoulder), 1522 (Nujol); UV: 260 (14800; $H_2O$).

**Example 96**

**3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 23, 3.3 g of the sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid (see Example 73a) for preparation), 1.0 g of isonicotinamide, 9.1 g of sodium iodide and 1.0 g of trichloroacetic acid are reacted in 6.1 ml of water, worked up, chromatographed and reprecipitated. The title compound is obtained; m.p. above 175° (with decomposition); IR: 2700—2500 (broad), 1778, 1720 (shoulder), 1688, 1610, 1570, 1520 (Nujol); UV: 260 (13000; $H_2O$).

**Example 97**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.8 g of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable

according to Example 97c) are reacted in 3.75 ml of $CH_2Cl_2$ and 1.32 ml of anisole with 15 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The title compound is obtained; m.p. above 170° (with decomposition); $[\alpha]_D^{20°}=+44°\pm1°$ (0.98% in $H_2O$); IR: 3660—2500 (broad), 1761, 1697, 1605, 1521 (Nujol); UV: 258 ( ; $H_2O$).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 2.07 g of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 97c) are reacted in 4.3 ml of $CH_2Cl_2$ and 1.52 ml of anisole with 17.25 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The title compound is obtained; m.p. above 170° (with decomposition); $[\alpha]_D^{20°}=+78°\pm1°$ (1.06% in $H_2O$); IR: 3660—2500 (broad), 1760, 1700, 1605, 1520 (Nujol); UV: 255 (12700; $H_2O$).

**c) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-ethanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 3 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-ethanesulphonylaminoacetic acid obtainable according to Example 97d) are reacted with 3 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 40 ml of tetrahydrofuran (0.73 g of hydroxybenzotriazole; three times 0.67 g of dicyclohexyl carbodiimide each time in 4 ml of tetrahydrofuran) and worked up. The resulting crude product is chromatographed over 450 g of silica gel [graduated column; eluant: toluene/ethyl acetate 3:2, 1:1 and 1:2 mixtures]. In so doing, the title compound having the 2R-configuration is eluted first (see Example 7d) for assignment of configuration); $[\alpha]_D^{20°}=-26°\pm1°$ (0.79% in $CHCl_3$); IR: 3530, 3420, 3300, 1778, 1715, 1698 (shoulder), 1582, 1530 ($CH_2Cl_2$); UV: 260 ( ; EtOH).

The next fractions consist of a mixture of the (2R)- and (2S)-title compounds. Finally, the uniform 2S-title compound is eluted; $[\alpha]_D^{20°}=-12°\pm1°$ (0.83% in $CHCl_3$); IR: 3530, 3420, 3300, 1775, 1715, 1695 (shoulder), 1582, 1530 ($CH_2Cl_2$); UV: 260 (16000; EtOH).

The starting material is prepared as follows:

**d) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-ethanesulphonylaminoacetic acid**

Analogously to Example 6c), 3 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetic acid are reacted in 30 ml of $CH_2Cl_2$ with 1.82 ml of ethanesulphonyl chloride (10. 5 ml of N,O-bis(trimethylsilyl)acetamide; 1.043 ml of pyridine) and worked up. The title compound is obtained and is further processed without being characterised.

**Example 98**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound, which is identical to that of Example 21, is obtained starting from 8.07 g (10 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 40 ml of absolute methylene chloride, with 8 ml of anisole and 40 ml of trifluoroacetic acid; m.p. above 175° (with decomposition); UV: 253 (10500; water); $[\alpha]_D^{20°}=+95°\pm1°$ (0.880% in water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 9.17 g (20 mmol) of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetic acid prepared according to Example 98c) and 7.3 g (20 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 200 ml of absolute tetrahydrofuran in the presence of 2.7 g of 1-hydroxybenzotriazole and 4.54 g of dicyclohexyl carbodiimide is stirred at room temperature for 16 hours. The dicyclohexylurea which is formed is filtered off and the filtrate is concentrated. The residue, dissolved in 600 ml of ethyl acetate, is washed with 0.5N hydrochloric acid and sodium chloride solution. After drying the organic phase with sodium sulphate, the solvent is removed in a rotary evaporator and the resulting crude product is purified over silica gel (30 times the amount) with methylene chloride/ethyl acetate (1:1) as eluant, to yield the title compound as an amorphous powder. TLC (silica gel, identification UV 366): $R_f$: approximately 0.25 (methylene chloride/ethyl acetate 1:1).

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetic acid**

60 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring at room temperature with the exclusion of moisture to a suspension of 22.82 g (60 mmol) of the (2R,S)-2-(2-aminoethane-

sulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid obtainable according to Example 13d) in 480 ml of absolute tetrahydrofuran. The reaction mixture is stirred for one hour at 65°, cooled to 0° and 7.1 ml of absolute pyridine and 7 ml of methanesulphonyl chloride are added. After a reaction period of 2 hours, 2.4 ml of pyridine and 2.3 ml of methanesulphonyl chloride are again added to the reaction mixture which is now at room temperature. After a reaction period of a further 16 hours, the solvent is removed in a rotary evaporator, the residue is dissolved in ethyl acetate and washed three times with cold 1N hydrochloric acid and three times with saturated sodium chloride solution. The organic phase, dried over sodium sulphate, is freed of solvent in a rotary evaporator, to yield the title compound as a beige amorphous powder which can be used in the next synthesis step without further purification. $R_f$ 96: 0.48 (silica gel, UV 366).

**Example 99**

**7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

600 mg of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid pivalate are stirred at 0° for 30 minutes in 6 ml of dimethylformamide. 10 ml of phosphate buffer at pH 8 are then added and the mixture is again stirred at 0° for 5 minutes. The mixture is then taken up in 25 ml of ethyl acetate, washed twice with saturated aqueous sodium chloride solution and dried over sodium sulphate. Filtration is then carried out and 1.6 ml of 0.7N HCl in methylene chloride are added. The amorphous precipitate which forms is decanted off, washed three times with hexane and dried at room temperature *in vacuo*. The material is then digested with ether, filtered off from the ether and again dried. The title compound, which still contains 0.5 g of dimethylformamide, is obtained; m.p. above 100° (with decomposition); $[\alpha]_D^{20°}=+60°\pm1°$ (0.810% in DMSO); UV: 255 (10300; $CH_3OH$).

**Example 100**

**a) The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the 1.5-hydrate starting from 7.03 g (8 mmol) of 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester prepared according to Example 100b), dissolved in 35 ml of methylene chloride, in the presence of 7 ml of anisole with 35 ml of trifluoroacetic acid; m.p. above 115° (with decomposition); $R_f$: 0.28 (silica gel, UV 366); $[\alpha]_D^{20°}=+48°\pm1°$ (0.826% in water); UV: 255 (11900; water).

**b) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained as an amorphous powder starting from 9.17 g (20 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethane-sulphonylamino)-acetic acid prepared according to Example 98c), dissolved in 200 ml of absolute tetrahydrofuran, in the presence of 2.7 g of 1-hydroxybenzotriazole and 4.54 g of dicyclohexyl carbodiimide with 8.77 g (20 mmol) of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. $R_f$: 0.58 (silica gel, UV 366; ethyl acetate).

**Example 101**

**3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethane-sulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 99, 1.9 g (3 mmol) of the sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid and 0.78 ml of iodomethyl pivalate are reacted in 19 ml of dimethylformamide and worked up, to yield the title compound containing 0.5 equivalent of dimethylformamide; m.p. above 95° (with decomposition); $[\alpha]_D^{20°}=+24°\pm1°$ (1.07% in DMSO); UV: 260 (12100 in methanol).

**Example 102**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the dihydrate starting from 7.15 g (7.5 mmol) of the 3-(1-methyl-1H-tetrazol-5-yl-thiomethyl)-7β-[(2R,S)-2-(2-BOC-amino-thiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester prepared according to Example 102b), dissolved in 37 ml of methylene chloride, in the presence of 7.2 ml of anisole with 37 ml of trifluoroacetic acid; m.p. above 123° (with decomposition); $R_f$: 0.25 (silica gel, UV 266); $[\alpha]_D^{20°}=-4°\pm1°$ (0.802% in water); UV: 260 (13450; water).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained as an amorphous powder starting from 9.17 g (20 mmol) of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylamino-ethanesulphonylamino)-acetic acid prepared according to Example 98c), dissolved in 200 ml of absolute tetrahydrofuran, in the presence of 2.7 g of 1-hydroxybenzotriazole and 4.54 g of dicyclohexyl carbodiimide with 19.1 g (20 mmol) of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. $R_f$: 0.50 (silica gel; UV 366, ethyl acetate).

**Example 103**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the dihydrate starting from 1.05 g (1.2 mmol) of the 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester prepared according to Example 103d), dissolved in 6 ml of methylene chloride, in the presence of 1 ml of anisole with 6 ml of trifluoroacetic acid; m.p. above 108° (with decomposition); $R_f$ 96: 0.22 (silica gel, UV 366); $[\alpha]_D^{20°}=+44°\pm1°$ (1.105% in water); UV: 255 (12600; water).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the 1.5-hydrate starting from 2.51 g (2.85 mmol) of the 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester prepared according to Example 103d), dissolved in 14 ml of methylene chloride, in the presence of 2.5 ml of anisole with 14 ml of trifluoroacetic acid; m.p. above 105° (with decomposition); $R_f$ 96: 0.22 (silica gel, UV 366); $[\alpha]_D^{20°}=+35°\pm1°$ (0.884% in water); UV: 255 (2000; water).

**c) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the dihydrate starting from 3.96 g (4.5 mmol) of the 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtained according to Example 103d), dissolved in 22.5 ml of methylene chloride, in the presence of 4 ml of anisole with 22.5 ml of trifluoroacetic acid; m.p. above 122° (with decomposition); $R_f$ 96: 0.22 (silica gel, UV 366); $[\alpha]_D^{20°}=+59°\pm1°$ (0.958% in water); UV 255 (13400; water).

**d) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained as a 2R,S-diastereoisomeric mixture starting from 9.17 g (20 mmol) of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methanesulphonylamino)-ethanesulphonylaminoacetic acid obtained according to Example 98c), dissolved in 200 ml of absolute tetrahydrofuran, in the presence of 2.7 g of 1-hydroxybenzotriazole and 4.53 g of dicyclohexyl carbodiimide with 8.8 g (20 mmol) of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. The crude product is chromatographed over silica gel (1000 g) with methylene chloride/ethyl acetate 1:1 and ethyl acetate as eluant, from which the title compounds having the 2R-configuration ($R_f$: 0.48 silica gel, ethyl acetate), 2R,S-configuration and 2S-configuration ($R_f$: 0.43 silica gel, ethyl acetate) can be isolated as an amorphous powder (see Example 7d) for assignment of configuration).

**Example 104**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

As a supplement to Example 67 and by analogy with Example 29a), the title compound is obtained as a yellowish powder in the form of the dihydrate by reacting 0.85 g (0.86 mmol) of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence

of 0.85 ml of anisole with 5 ml of trifluoroacetic acid in 5 ml of methylene chloride; m.p. above 155° (with decomposition); $R_f$: approximately 0.45 (silica gel Opti-UPC 12, water/acetonitrile 4:1); $[\alpha]_D^{20°}$=+5°±1° (0.673% in water); UV: 258 (23200 in water).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

As a supplement to Example 67 and by analogy with Example 29a), the title compound is obtained as a pale yellowish powder in the form of the dihydrate by reacting 0.8 g (0.81 mmol) of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.8 ml of anisole with 4 ml of trifluoroacetic acid in 4 ml of methylene chloride; m.p. above 112° (with decomposition); $R_f$: approximately 0.45 (silica gel Opti-UPC 12, water/acetonitrile 4:1); $[\alpha]_D^{20°}$=+36°±1° (0.515% in water); UV: 256 (21900 in water).

**c) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the crude product is obtained as a 2R,S-diastereoisomeric mixture by treating 4.52 g (8.0 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetic acid with 3.51 g (8.0 mmol) of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.08 g of 1-hydroxybenzotriazole and 1.81 g of dicyclohexyl carbodiimide in 80 ml of tetrahydrofuran. The crude product is chromatographed over silica gel (300 g) with methylene chloride/ethyl acetate 7:3 as eluant and, from the first fractions, the title compound having the 2R-configuration is eluted ($R_f$: 0.38) and, from the next fractions, the title compound having the 2S-configuration ($R_f$: 0.33, silica gel, methylene chloride/ethyl acetate 1:1) is eluted.

**Example 105**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as a yellowish powder in the form of the dihydrate by reacting 3.06 g (3.2 mmol) of the 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtained according to Example 105c) in the presence of 15 ml of anisole with 3 ml of trifluoroacetic acid in 15 ml of methylene chloride; m.p. above 150° (with decomposition); $[\alpha]_D^{20°}$=+52°±1° (1.037% in water); UV: 258 (28500 in water).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as a yellowish powder in the form of the dihydrate by reacting 2.6 g (2.7 mmol) of the 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtained according to Example 105d) in the presence of 2.6 ml of anisole with 13 ml of trifluoroacetic acid in 13 ml of methylene chloride; m.p. above 150° (with decomposition); $[\alpha]_D^{20°}$=+38°±1° (1.03% in water); UV: 258 (28900 in water).

**c) 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 3.5 g (3.55 mmol) of the 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtained according to Example 104c) in 70 ml of ethyl acetate is hydrogenated at room temperature under normal pressure in the presence of 1.7 g of 10% palladium-on-carbon catalyst. Filtration and washing with ethyl acetate is carried out, the filtrate is concentrated and the title compound is obtained as a yellow powder. $R_f$: 0.44 (silica gel, UV 266; ethyl acetate).

**d) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazo-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 2.96 g (3 mmol) of the 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtained according to Example 104c) in 600 ml of ethyl acetate is hydrogenated at room temperature under normal pressure in the presence of 1.5 g of 10% palladium-

on-carbon catalyst. After the absorption of 3 equivalents of hydrogen gas, the catalyst is filtered off and washed with ethyl acetate. The filtrate is concentrated to yield the title compound. $R_f$: 0.46 (silica gel, UV 366; ethyl acetate).

**Example 106**

**a) The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-amino-benzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained as a yellowish powder in the form of the 1.5-hydrate by reacting 3.75 g (2.9 mmol) of 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-amino-thiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 3.8 ml of anisole with 19 ml of trifluoroacetic acid in 19 ml of methylene chloride; m.p. above 152° (with decomposition); $[\alpha]_D^{20°}=+48°\pm1°$ (0.869% in water); UV: 258 (28500 in water).

**b) 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonyl-amino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 7.5 g (7.6 mmol) of the 3-acetoxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtained according to Example 39b) is hydrogenated at room temperature under normal pressure in the presence of 3.5 g of 10% palladium-on-carbon catalyst. After the absorption of 3 equivalents of hydrogen gas, the catalyst is filtered off and washed with ethyl acetate. The solvent is removed in a rotary evaporator to yield the title compound. $R_f$: 0.58 (silica gel, UV 366, ethyl acetate).

**Example 107**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-(2,4-dinitro-benzenesulphonylamino)-ethanesulphonylamino)-2-(2-amino-thiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the 1.5-hydrate of the title compound is obtained as a yellowish powder by reacting 5.6 g (5.15 mmol) of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 5.6 ml of anisole with 20 ml of trifluoroacetic acid in 28 ml of methylene chloride.

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-(2,4-dinitrobenzenesulphonyl-amino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained as a pale yellow amorphous powder by treating 6.1 g (10 mmol) of the (2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonyl-amino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid obtained according to Example 40c) with 4.94 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 1.35 g of 1-hydroxybenzotriazole and 2.26 g of dicyclohexyl carbodiimide in 120 ml of tetrahydrofuran (reaction period: 16 hours at room temperature). $R_f$: 0.70 (silica gel, UV 366; ethyl acetate).

**Example 108**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-(2,4-dinitrobenzene-sulphonylamino)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the dihydrate of the title compound is obtained as a yellowish powder by reacting 7.0 g (6.78 mmol) of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-(2,4-dinitrobenzene-sulphonylamino)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 7.0 ml of anisole with 35 ml of trifluoroacetic acid in 35 ml of methylene chloride; $[\alpha]_D^{20°}=+40°\pm1°$ (0.977% in water); $R_f$: 0.10 (silica gel Opti-UPC 12, water); UV: 250 (23000 in water).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethane-sulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenyl-methyl ester**

Analogously to Example 29b), the title compound is obtained as a pale yellow amorphous powder by treating 9.17 g (15 mmol) of the (2R,S)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethane-sulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid obtained according to Example 40c) with 6.6 g of carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.03 g of 1-hydroxybenzotriazole and 3.4 g of dicyclohexyl carbodiimide in 200 ml of tetrahydrofuran (reaction period: 16 hours at room temperature); TLC (silica gel, identification UV 266): $R_f$ 0.25 (methylene chloride/ethyl acetate 1:1).

**Example 109**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate by reacting 5.02 g (5.9 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 5 ml of anisole with 25 ml of trifluoroacetic acid in 25 ml of methylene chloride; m.p. above 150° (with decomposition); $[\alpha]_D^{20°}=+24°\pm1°$ (0.362% in water); UV: 246 (19800; water); $R_f$: 0.33 (silica gel Opti-UPC 12, water/acetonitrile 4:1).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound is obtained by treating 10.06 g (20 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylamino)-acetic acid with 7.33 g (20 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.7 g of 1-hydroxybenzotriazole and 4.54 g of N,N'-dicyclohexyl carbodiimide in 200 ml of tetrahydrofuran (reaction period: 16 hours at room temperature) $R_f$: 0.70 (methylene chloride 1:1).

Preparation of the starting material:

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylaminoacetic acid**

109 ml of N,O-bis(trimethylsilyl)acetamide are added while stirring under a nitrogen atmosphere with the exclusion of moisture to a suspension of 40.95 g (0.15 mol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-aminoacetic acid in 500 ml of absolute tetrahydrofuran. After a reaction period of one hour at 60°, the reaction mixture is cooled to 0°, 13 ml of pyridine and 48 g (0.18 mol) of 2,4-dinitrobenzenesulphonyl chloride are added and the whole is then stirred for 16 hours at room temperature. After removing the solvent, the residue is taken up in 1500 ml of ethyl acetate and washed three times with 1.0N hydrochloric acid and three times with saturated aqueous sodium chloride solution. After drying over sodium sulphate, the solvent is removed in a rotary evaporator. The residue is made into a slurry in ether and filtered, to yield the title compound as an amorphous powder. $R_f$: 0.35 (silica gel, UV 366; chloroform/methanol/acetic acid 75:22:13).

**Example 110**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate by reacting 2.78 g (3 mmol) of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.8 ml of anisole with 14 ml of trifluoroacetic acid in 14 ml of methylene chloride; m.p. above 131° (with decomposition); $R_f$ 96: 0.38 (silica gel, UV 366); $[\alpha]_D^{20°}=+88°\pm1°$ (0.497% in water); UV: 250 (22300 in water).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate by reacting 3.51 g (2.8 mmol) of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2,4-dinitrobenzenesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 3.5 ml of anisole with 17.5 ml of trifluoroacetic acid in 17.5 ml of methylene chloride; m.p. above 130° (with decomposition); $R_f$ 96: approximately 0.30 (silica gel, UV 266); $[\alpha]_D^{20°}=-36°\pm1°$ (0.556% in water); UV: 250 (21800; water).

**c) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the crude product is obtained as a 2R,S-diastereoisomeric mixture by treating 10.06 g (20 mmol) of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetic acid obtained according to Example 109c) with 8.79 g (20 mmol) of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.7 g of 1-hydroxybenzotriazole and 4.54 g of dicyclohexyl carbodiimide in 80 ml of tetrahydrofuran (reaction period: 16 hours at room temperature). The crude product is chromatographed over silica gel (1000 g) with toluene/ethyl acetate 4:1 as eluant and, in the first fractions, the title compound having the 2R-configuration ($R_f$: 0.63) is eluted and, in the last fractions, the title compound having the 2S-configuration ($R_f$: 0.15, silica gel, methylene chloride/ethyl acetate 1:1) is eluted.

**Example 111**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound in the form of the 1.5-hydrate is obtained starting from 1.85 g (2.2 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 10 ml of methylene chloride, in the presence of 1.85 ml of anisole with 10 ml of trifluoroacetic acid. M.p. above 170° (with decomposition); $R_f$ 96: 0.38 (silica gel, UV 366); $[\alpha]_D^{20°}$=+98°±1° (0.890% in water); UV: 250 (10600, water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained in the form of an amorphous powder starting from 2.47 g (5 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetic acid, dissolved in 60 ml of absolute tetrahydrofuran, in the presence of 0.68 g of 1-hydroxybenzotriazole and 1.13 g of dicyclohexyl carbodiimide with 1.83 g (5 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. $R_f$: 0.73 (silica gel, UV 366; ethyl acetate).

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 98c), after the esterification of 11.41 g (30 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 30 ml of N,O-bis(trimethylsilyl)-acetamide in 150 ml of tetrahydrofuran and after reaction with 5.87 g of difluoromethanesulphonyl chloride in the presence of 3.1 ml of pyridine there is obtained the title compound which can in addition be purified over silica gel (300 g) with methylene chloride/ethyl acetate as eluant. $R_f$ 96: 0.71 (silica gel, UV 366).

**Example 112**

**a) The sodium salt of 3-(1-methyl-1H-tetrazol-5-yl-thiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the dihydrate starting from 2.6 g (2.68 mmol) of 3-(1-methyl-1H-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 13 ml of methylene chloride, in the presence of 2.6 ml of anisole and 13 ml of trifluoroacetic acid. M.p. above 150° (with decomposition); $R_f$ 96: 0.38 (silica gel, UV 366); $[\alpha]_D^{20°}$=−4°±1° (0.984% in water); UV 258 (14400, water).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained in the form of an amorphous powder starting from 2.47 g (5 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetic acid, dissolved in 60 ml of absolute tetrahydrofuran, in the presence of 0.68 g of 1-hydroxybenzotriazole and 1.13 g of dicyclohexyl carbodiimide with 2.47 g (5 mmol) of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. $R_f$: 0.65 (silica gel, UV 366, ethyl acetate).

**Example 113**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the 1.8 hydrate starting from 1.5 g (1.64 mmol) of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 7.5 ml of methylene chloride, in the presence of 1.5 ml of anisole with 7.5 ml of trifluoroacetic acid. M.p. above 145° (with decomposition); $R_f$ 96: 0.34 (silica gel, UV 366); $[\alpha]_D^{20°}$=+50°±1° (0.921% in water); UV 256 (13000, water).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained in the form of an amorphous powder starting from 1.7 g (3.44 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-difluoromethanesulphonylaminoethanesulphonylamino)-acetic acid, dissolved in 40 ml of absolute tetra-

hydrofuran, in the presence of 0.47 g of 1-hydroxybenzotriazole and 0.78 g of dicyclohexyl carbodiimide with 1.51 g (3.44 mmol) of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. $R_f$: 0.51 (silica gel, UV 366, ethyl acetate).

**Example 114**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-difluoromethanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the 2.5 hydrate starting from 3.5 g (4.76 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-difluoromethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 17.5 ml of methylene chloride, in the presence of 3.5 ml of anisole with 17.5 ml of trifluoroacetic acid. M.p. above 161° (with decomposition); $R_f$ 96: 0.30 (silica gel, UV 366); $[\alpha]_D^{20°}=+106°\pm1°$ (0.746% in water), UV 252 (10500, water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-difluoromethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained in the form of an amorphous powder starting from 1.94 g (5 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-difluoromethanesulphonylaminoacetic acid, dissolved in 40 ml of absolute tetrahydrofuran, in the presence of 0.68 g of 1-hydroxybenzotriazole and 1.13 g of dicyclohexyl carbodiimide with 1.89 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. $R_f$: 0.58 (silica gel, UV 366, ethyl acetate).

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-difluoromethanesulphonylaminoacetic acid**

Analogously to Example 98c), after the esterification of 13.65 g (50 mmol) of (2R,S)-2-amino-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 40 ml of N,O-bis(trimethyl)acetamide in 200 ml of tetrahydrofuran and after reaction with 9.03 g of difluoromethanesulphonyl chloride in the presence of 4.8 ml of pyridine, there is obtained the title compound which can in addition be purified over silica gel (420 g) with methylene chloride/ethyl acetate as eluant. $R_f$ 96: 0.61 (silica gel, UV 366).

**Example 115**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-difluoromethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the dihydrate starting from 6.47 g (8.0 mmol) of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-difluoromethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 32.5 ml of methylene chloride, in the presence of 6.5 ml of anisole with 32.5 ml of trifluoroacetic acid. M.p. above 142° (with decomposition); $R_f$ 96: 0.28 (silica gel, UV 366); $[\alpha]_D^{20°}=+57°\pm1°$ (1.152% in water); UV 257 (13000, water).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-difluoromethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained in the form of an amorphous powder starting from 4.65 g (12 mmol) of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-difluoromethanesulphonylaminoacetic acid obtained according to Example 114c), dissolved in 95 ml of absolute tetrahydrofuran, in the presence of 1.62 g of 1-hydroxybenzotriazole and 2.72 g of dicyclohexyl carbodiimide with 5.3 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. $R_f$: 0.58 (silica gel, UV 366; ethyl acetate).

**Example 116**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-pyrid-3-ylsulphonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the 1.5-hydrate starting from 4.0 g (4.5 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-pyrid-3-ylsulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 20 ml of methylene chloride, in the presence of 3.3 ml of anisole with 20 ml of trifluoroacetic acid. M.p. above 164° (with decomposition); $R_f$ 96: 0.30 (silica gel, UV 366); $[\alpha]_D^{20°}=+80°\pm1°$ (0.779% in water); UV 254 (12300, water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-pyrid-3-ylsulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained in the form of the amorphous powder starting from 4.7 g (9 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-pyrid-3-ylsulphonylaminoethanesulphonylaminoacetic acid, dissolved in 90 ml of absolute tetrahydrofuran, in the presence of 1.22 g of 1-hydroxybenzotriazole and 2.10 g of dicyclohexyl carbodiimide with 3.5 g (9 mmol) of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester (reaction time 5 hours). $R_f$: 0.45 (silica gel, UV 366; methylene chloride/ethyl acetate 1:1).

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-pyrid-3-ylsulphonylaminoethanesulphonylamino)-acetic acid**

Analogously to Example 98c), the title compound is obtained after the esterification of 7.61 g (20 mmol) of (2R,S)-2-(2-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 16 ml of N,O-bis(trimethylsilyl)acetamide in 60 ml of tetrahydrofuran and after reaction with 5.14 g of 3-pyridinesulphonyl chloride hydrochloride in the presence of 4.9 ml of N-methylmorpholine. $R_f$ 96: 0.40 (silica gel, UV 366).

**Example 117**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-pyrid-3-ylsulphonylamino-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 21a), the title compound is obtained in the form of the dihydrate starting from 3.43 g (4.5 mmol) of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-pyrid-3-ylsulphonylamino-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 20 ml of methylene chloride, in the presence of 3.3 ml of anisole and 20 ml of trifluoroacetic acid. M.p. above 179° (with decomposition); $R_f$ 96: 0.35 (silica gel, UV 366); $[\alpha]_D^{20°}$=+94°±1° (0.929% in water); UV 254 (11800, water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-pyrid-3-ylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 98b), the title compound is obtained in the form of an amorphous powder starting from 2.9 g (7 mmol) of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-pyrid-3-ylsulphonyl-aminoacetic acid, dissolved in 70 ml of absolute tetrahydrofuran, in the presence of 0.95 g of 1-hydroxybenzotriazole and 1.6 g of dicyclohexyl carbodiimide with 2.6 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester. $R_f$: 0.38 (silica gel, UV 366; methylene chloride/ethyl acetate (1:1).

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-pyrid-3-ylsulphonylaminoacetic acid**

Analogously to Example 98c), and title compound is obtained after the esterification of 2.73 g (10 mmol) of (2R,S)-2-amino-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 30 ml of N,O-bis(trimethylsilyl)acetamide in 30 ml of tetrahydrofuran and after reaction with 2.57 g of 3-pyridine-sulphonyl chloride hydrochloride in the presence of 1.6 ml of N-methylmorpholine. $R_f$ 96: 0.49 (silica gel, UV 266).

**Example 118**

**a) The sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-(2-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate starting from 1.04 g (1 mmol) of 3-acetoxymethyl-7β-[(2R,S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 5 ml of methylene chloride, in the presence of 1 ml of anisole with 5 ml of trifluoroacetic acid. M.p. above 150° (with decomposition); $R_f$: 0.25 (silica gel Opti UPC 12, UV 366, water/acetonitrile 4:1); $[\alpha]_D^{20°}$=+57°±1° (1.183% in water); UV 254 (18500, water).

**b) The sodium salt of 3-acetoxymethyl-7β-[(2R)-2-(2-(2-aminothiazol-4-ylacetamido)-ethane-sulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate starting from 1.60 g (1.54 mmol) of 3-acetoxymethyl-7β-[(2R)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 8 ml of methylene chloride, in the presence of 1.6 ml of anisole with 8 ml of trifluoroacetic acid. M.p. above 151° (with decomposition); $R_f$: 0.25 (silica gel Opti UPC 12, UV 366, water/acetonitrile 4:1); $[\alpha]_D^{20°}$=+39°±1° (1.111% in water); UV 254 (17700, water).

**c) The sodium salt of 3-acetoxymethyl-7β-[(2S)-2-(2-(2-aminothiazol-4-ylacetamido)-ethane-sulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate starting from 1.90 g (1.83 mmol) of 3-acetoxymethyl-7β-[(2S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 9.5 ml of methylene chloride, in the presence of 1.9 ml of anisole with 9.5 ml of trifluoroacetic acid. M.p. above 150° (with decomposion); $R_f$: 0.25 (silica gel Opti UPC 12, UV 366, water/acetonitrile 4:1); $[\alpha]_D^{20°}$=+61°±1° (1.473% in water); UV 254 (18800, water).

**d) 3-acetoxymethyl-7β-[(2R,S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester,**
**3-acetoxymethyl-7β-[(2R)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and**
**3-acetoxymethyl-7β-[(2S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound in the form of a 2R,S-diastereoisomeric mixture is obtained starting from 3.5 g (5.7 mmol) of the (2R,S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid obtained in accordance with Example 29c), dissolved in 60 ml of tetrahydrofuran, in the presence of 0.77 g of 1-hydroxybenzotriazole and 1.29 g of dicyclohexyl carbodiimide with 2.5 g (5.7 mmol) of 3-acetoxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester (reaction time 16 hours at room temperature). The crude product is chromatographed over silica gel (280 g) with methylene chloride/ethyl acetate 1:1 as eluant, the title compound with the 2R-configuration ($R_f$: 0.58, silica gel, ethyl acetate) being eluted in the first fractions, the title compound with the 2R,S-configuration in the following fractions, and the title compound with the 2S-configuration in the last fractions ($R_f$: 0.48, silica gel, ethyl acetate).

**Example 119**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-(2-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the dihydrate starting from 4.17 g (4 mmol) of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 20 ml of methylene chloride, in the presence of 4 ml of anisole with 20 ml of trifluoroacetic acid. M.p. above 155° (with decomposition); $R_f$: 0.20 (silica gel Opti UPC 12, UV 366, water/acetonitrile 4:1); $[\alpha]_D^{20°}=+34°\pm1°$ (1.341% in water); UV 256 (18500, water).

**b) The sodium salt of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-(2-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 29a), the title compound is obtained in the form of the 2.5 hydrate starting from 4.17 g (4 mmol) of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 20 ml of methylene chloride, in the presence of 4 ml of anisole with 20 ml of trifluoroacetic acid. M.p. above 160° (with decomposition); $R_f$: 0.18 (silica gel Opti-UPC 12, UV 366, water/acetonitrile 4:1); $[\alpha]_D^{20°}=+57°\pm1°$ (0.884% in water); UV 257 (18500, water).

**c) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and**
**3-carbamoyloxymethyl-7β-[(2S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 29b), the title compound in the form of a 2R,S-diastereoisomeric mixture is obtained starting from 7.44 g (12 mmol) of the (2R,S)-2-(2-(2-BOC-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid obtained in accordance with Example 29c), dissolved in 120 ml of tetrahydrofuran, in the presence of 1.62 g of 1-hydroxybenzotriazole and 2.72 g of dicyclohexyl carbodiimide with 5.27 g (12 mmol) of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester (reaction time 16 hours at room temperature). The crude product is chromatographed over silica gel (700 g) with methylene chloride/ethyl acetate 1:1 as eluant, and from this the title compounds with the 2R-configuration ($R_f$: 0.33, silica gel, ethyl acetate) and the 2S-configuration ($R_f$: 0.25 silica gel, ethyl acetate) are each isolated in the form of amorphous powder.

**Example 120**

**a) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 13a), the title compound is obtained in the form of the 1.5-hydrate starting from 3.6 g (4 mmol) of 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 16 ml of absolute methylene chloride, in the presence of 3.2 ml of anisole and 16 ml of trifluoroacetic acid. M.p. above 140° (with decomposition); $R_f$: 0.75 (silica gel Opti UPC 12, water/acetonitrile 4:1); UV: 254 (13800, 0.1N HCl).

**b) 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminoethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 13a), the title compound is obtained in the form of the 1.5-hydrate starting from 4.96 g (5.5 mmol) of 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, dissolved in 22 ml of absolute methylene chloride in the presence of 4.4 ml of anisole and 22 ml of trifluoroacetic acid. M.p. above 142° (with decomposition); $R_f$: 0.75 (silica gel Opti UPC 12, water/acetonitrile 4:1); UV 254 (13600, 0.1N HCl).

**c) 3-carbamoyloxymethyl-7β-[(2R)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester and 3-carbamoyloxymethyl-7β-[(2S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 13b), the crude product is obtained in the form of a 2R,S-diastereoisomeric mixture by treating 9.6 g (20 mmol) of (2R,S)-2-(2-BOC-aminoethanesulphonylamino)-2-(2-BOC-aminothiazol-4-yl)-acetic acid with 8.79 g (20 mmol) of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.7 g of 1-hydroxybenzotriazole and 4.54 g of dicyclohexyl carbodiimide in 200 ml of tetrahydrofuran. The crude product is chromatographed over silica gel (1000 g) with methylene chloride/ethyl acetate 7:3 and 1:1 as eluant, and the title compounds with the 2R-configuration ($R_f$: 0.65) and the 2S-configuration ($R_f$: 0.55, silica gel, diethyl ether/ethyl acetate 1:1) are obtained.

**Example 121**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-phenylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 1.9 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-phenylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 40 ml of trifluoroacetic acid in 1.0 ml of anisole and 4 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 176° (with decomposition). IR: 3320 (broad), 3200, 1775 (shoulder), 1760, 1745 (shoulder), 1680, 1645, 1600, 1375, 1365, 1325 (shoulder), 1145 (in Nujol); $R_f$: ca. 0.74 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-phenylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

6.0 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-phenyl-2-trichloroethoxycarbonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester, produced analogously to Example 42 c)-e), are treated in 60 ml of acetonitrile/glacial acetic acid (1:1) with 20.0 g (2x10.0 g) of zinc dust, and worked up analogously to Example 13d) yielding the title compound in the form of a foam. $R_f$: approximately 0.43 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/chloroform/ethyl acetate 1:1:1+1% ethanol).

**Example 122**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(3-(2-furoyl)-ureido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 1.9 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(3-(2-furoyl)-ureido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 50 ml of trifluoroacetic acid in 0.40 ml of anisole and 5 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p.: from 196° (with decomposition). IR: 3310 (broad), 3200, 1765 (broad), 1690 (broad), 1600 (broad), 1375, 1365, 1340 (shoulder), 1175, 1150 (in Nujol); $R_f$: approximately 0.38 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(3-(2-furoyl)-ureido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 3.50 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in 100 ml of ethyl acetate is prepared and cooled to +3° and, while stirring and cooling, a solution of 0.85 g of 2-furoyl isocyanate in 50 ml of ethyl acetate is added dropwise thereto in the course of one hour and the reaction mixture is then stirred for 5 hours in an ice bath. Subsequently the ethyl acetate solution is washed with water, dried over sodium sulphate, concentrated in a rotary evaporator at 50° and the crude product is purified by chromatography over 60 times the amount of silica gel. Eluant: methylene chloride with 25 to 40% of methyl acetate. The title compound is obtained in the form of a foam. $R_f$: approximately 0.27 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/chloroform/ethyl acetate 1:1:1+5% ethanol).

**Example 123**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-ethoxycarbonylureido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 1.29 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(3-ethoxycarbonylureido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 50 ml of trifluoroacetic acid in 0.40 ml of anisole and 5 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 232° with decomposition; IR: 3320 (broad), 3200, 1775 (shoulder), 1760 (broad), 1730, 1690 (broad), 1640, 1605, 1375, 1365, 1175 (shoulder), 1145 (in Nujol); $R_f$: approximately 0.42 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(3-ethoxycarbonylureido)-ethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 122b), the title compound is obtained by reacting 3.40 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 2.5 ml of ethoxycarbonyl isocyanate in 150 ml (100 ml and 50 ml) of ethyl acetate. The crude product is purified by chromatography over 20 times the amount of silica gel. Eluant: methylene chloride with 15 to 25% of methyl acetate. $R_f$: approximately 0.16 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/chloroform/ethyl acetate 1:1:1+3% ethanol).

**Example 124**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-benzenesulphonylureido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 1.5 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(3-benzenesulphonylureido)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 50 ml of trifluoroacetic acid in 0.40 ml of anisole and 5 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 200° with decomposition. IR: 3320 (broad), 3200, 1785, 1760, 1685, 1640 (shoulder), 1600 (broad), 1375, 1365, 1350 (shoulder), 1165 (shoulder), 1135 (in Nujol); $R_f$: approximately 0.37 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-(3-benzenesulphonylureido)-ethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 122b), the title compound is obtained by reacting 3.50 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 1.10 g of benzenesulphonyl isocyanate in 120 ml of ethyl acetate (100 ml and 20 ml). The crude product is purified by chromatography over 20 times the amount of silica gel. Eluant: methylene chloride with 20 to 30% of methyl acetate. $R_f$: approximately 0.14 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/chloroform/ethyl acetate 1:1:1+3% ethanol).

**Example 125**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 6 g of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 100 ml of trifluoroacetic acid in 2.50 ml of anisole and 10 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 148° with decomposition. IR: 3320 (broad), 3200, 1785 (shoulder), 1760, 1700 (broad), 1605 (broad), 1380, 1330, 1145, 1115 $cm^{-1}$ (in Nujol). $R_f$: 0.37 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 42c), the title compound is obtained by reacting 4.30 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetic acid with 4.0 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 2.40 g (2×1.20 g) of N,N'-dicyclohexyl carbodiimide in a total of 110 ml of tetrahydrofuran. The crude product is purified by chromatography over 25 times the amount of silica gel. Eluant: methylene chloride with 25 to 45% of methyl acetate. $R_f$: approximately 0.33 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/ethanol 9:1).

**Example 126**

**7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 1.90 g of the sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-

(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid and 0.90 g of iodomethyl pivalate are reacted in 12 ml of N,N-dimethylformamide and worked up. M.p. from 112° with decomposition. $R_f$: approximately 0.36 (silica gel Opti-UPC 12, UV 366, acetonitrile/water 1:1).

**Example 127**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 3.1 g of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 46 ml of trifluoroacetic acid in 1.10 ml of anisole and 7.5 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 180° with decomposition. IR: 3330 (broad), 3190 (broad), 1785 (shoulder), 1765, 1695 (broad), 1610 (broad), 1375, 1365, 1325, 1155, 1130 (shoulder) (in Nujol). $R_f$: approximately 0.24 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 42c), the title compound is obtained by reacting 2.0 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-methylaminoethanesulphonylamino)-acetic acid (for preparation see Example 79c)) and 2.0 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.37 g of 1-hydroxybenzotriazole and 1.30 g (0.70 and 0.60 g) of N,N'-dicyclohexyl carbodiimide in 90 ml of tetrahydrofuran. The crude product is purified by chromatography over 40 times the amount of silica gel. Eluant: methylene chloride/methyl acetate (7:3). $R_f$: approximately 0.32 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/ethyl acetate 1:1).

**Example 128**

**a) The disodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-sulphoaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 3.1 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-sulphoaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 40 ml of trifluoroacetic acid in 1.25 ml of anisole and 6 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 205° with decomposition. IR: 3420 (broad), 3340 (shoulder), 3200 (broad), 1780 (shoulder), 1755, 1680, 1635 (shoulder), 1600, 1360, 1325 (shoulder), 1180, 1145 (in Nujol), $R_f$: approximately 1.18 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-sulphoaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

A solution of 5.0 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester in 40 ml of methylene chloride is cooled to +2°, 2.7 ml of N-methyl morpholine are added, while stirring and cooling 3.6 ml of chlorosulphonic acid trimethylsilyl ester are added dropwise in the course of 5 minutes, and the reaction mixture is stirred at room temperature for 4 hours. The suspension is then diluted with ethyl acetate, the methylene chloride is removed in a rotary evaporator at 50°, and the ethyl ester solution is washed in succession with 20% citric acid solution and water (twice). The organic phase is dried over sodium sulphate, filtered and concentrated in a rotary evaporator at 50°. The crude product is purified by chromatography over 30 times the amount of silica gel. Eluant: chloroform/methanol/32% aqueous acetic acid 15:4:1. The title compound is obtained in the form of a foam. $R_f$: approximately 0.36 (silica gel, UV 366, chloroform/methanol/32% aqueous acetic acid 15:4:1).

**Example 129**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 1.9 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 60 ml of trifluoroacetic acid in 0.70 ml of anisole and 5 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 210° with decomposition. IR: 3300 (broad), 3190 (broad), 1775 (shoulder), 1755 (broad), 1680, 1640 (shoulder), 1600 (broad), 1375, 1365, 1150, 1120 (shoulder) (in Nujol). $R_f$: approximately 0.27 (silica gel Opti-UPC 12, UV 366, acetonitrile with 5% water).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 42a), the title compound is obtained by reacting 1.50 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetic acid and 1.50 g of 7β-amino-3-cephem-4-carboxylic acid in the presence of 1.0 g (2×0.50 g) of N,N'-dicyclohexyl carbodiimide in a mixture of 20 ml of tetrahydrofuran and 10 ml of N,N-dimethylformamide. The crude product is purified by chromatography over 20 times the amount of silica gel; eluant: methylene chloride with 5% of methyl acetate; the title compound is obtained in the form of a foam. $R_f$: approximately 0.70 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/chloroform/ethyl acetate 1:1:1+3% ethanol).

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetic acid**

40 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetic acid ethyl ester are dissolved in 350 ml of ethanol, while stirring and cooling gently 350 ml of 2N sodium hydroxide solution are added dropwise in the course of 20 minutes, and the reaction mixture is stirred at room temperature. After a reaction time of 2 hours, a further 100 ml of 2N sodium hydroxide solution is added dropwise to the clear, dark-orange coloured solution. After a total reaction time of 5.5 hours at room temperature, the pH of the mixture is adjusted to 7.5 with 10% hydrochloric acid, the majority of the ethanol is distilled off in a rotary evaporator at 50° and the aqueous solution is extracted with diethyl ether. The aqueous phase is then separated off, covered with a layer of ethyl acetate, cooled in an ice bath, while stirring and cooling rendered acidic (pH 2.0) by the dropwise addition of 20% phosphoric acid, and extracted twice with ethyl acetate. The organic phases are combined, washed twice with water, dried over sodium sulphate, filtered and concentrated in a rotary evaporator at 50°. The oily residue solidifies when mixed with a mixture of methylene chloride/petroleum ether (1:1). M.p. 119—122°. $R_f$: approximately 0.64 (silica gel, UV 366, n-butanol/glacial acetic acid/water 67:10:23).

**d) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetic acid ethyl ester**

A solution of 50 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine ethyl ester in 400 ml of dioxan and 45 ml of N-methylmorpholine is cooled to +10° and, while stirring virgorously and cooling, a solution of 40 g of 2-bromoethanesulphonyl chloride, produced as specified by C.S. Marcel *et al.*, J. Am. Chem. Soc., *49*, 1833 (1927), in 100 ml of dioxan is added dropwise in the course of 30 minutes. The reaction mixture is stirred at room temperature for 5 hours. The majority of the solvent is then evaporated off in a rotary evaporator at 50° and the suspension remaining is diluted with ethyl acetate and washed in succession with 20% citric acid solution, water, 1N sodium bicarbonate solution and water (3 times). The organic phase is dried over sodium sulphate, filtered and concentrated in a rotary evaporator at 50°. The crude product is purified by chromatography over 10 times the amount of silica gel and the title compound is obtained in the form of a foam. $R_f$: approximately 0.46 (silica gel, UV 366, toluene/ethyl acetate 1:1).

**Example 130**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 1.8 g of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 40 ml of trifluoroacetic acid in 1.0 ml of anisole and 4 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 168° with decomposition. IR: 3330 (broad), 3190, 1785 (shoulder), 1760, 1700 (broad), 1610 (broad), 1620, 1375, 1365 (weak), 1325, 1150, 1120 (in Nujol). $R_f$: approximately 0.24 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 42c), the title compound is obtained by reacting 1.30 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(vinylsulphonylamino)-acetic acid (for preparation see Example 129c)) and 1.70 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in the presence of 0.90 g (0.50 g and 0.40 g) of N,N'-dicyclohexyl carbodiimide in a total of 40 ml of tetrahydrofuran. The crude product is purified by chromatography over 25 times the amount of silica gel, eluant methylene chloride with 15 to 20% of methyl acetate, and the title compound is obtained in the form of a foam. $R_f$: approximately 0.18 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/chloroform/ethyl acetate 1:1:1+3% ethanol).

**Example 131**

**a) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

40 ml of trifluoroacetic acid are added to a suspension of 2.20 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl-2-(2-BOC-methylaminoethanesulphonyl-

amino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester in 0.90 ml of anisole and 5 ml of methylene chloride, the reaction mixture is stirred for 45 minutes at room temperature with the exclusion of atmospheric moisture, and is then poured onto an ice-cold mixture of 800 ml of petroleum ether and 200 ml of diethyl ether, the trifluoroacetate salt being precipitated. It is filtered with suction, washed with a mixture of petroleum ether and diethyl ether and dried at room temperature under a high vacuum. The trifluoroacetate salt is dissolved in approximately 300 ml of ethyl acetate and the solution is washed in succession with 1N sodium bicarbonate solution (2×60 ml) and soda solution. The organic phase is dried over sodium sulphate, filtered, excess hydrogen chloride in methylene chloride is added, and the whole is concentrated to approximately 50 ml in a rotary evaporator at 20—30°. The resulting title compound is filtered with suction, washed with ethyl acetate and diethyl ether, and dried at room temperature under a high vacuum. M.p. from 110° with decomposition. IR: 3180 (broad), 1785 (shoulder), 1775, 1750, 1690, 1625, 1375, 1365 (shoulder), 1335, 1150, 1115 (in Nujol). $R_f$: approximately 0.28 (silica gel Opti-UPC 12, UV 366, acetonitrile/water 4:1).

**b) 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester**

Analogously to Example 42c), the title compound is obtained by reacting 2.60 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-BOC-methylaminoethanesulphonylamino)-acetic acid (for preparation see Example 79c)) and 1.90 g of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid pivaloyloxymethyl ester in the presence of 0.32 g of 1-hydroxybenzotriazole and 1.90 g (2×0.95 g) of N,N'-dicyclohexyl carbodiimide in a total of 70 ml of tetrahydrofuran. The crude product is purified by chromatography over 45 times the amount of silica gel, eluant methylene chloride/methyl acetate (4:1), and the title compound is obtained in the form of a foam. $R_f$: approximately 0.26 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/ethyl acetate 1:1).

**Example 132**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-dimethylaminosulphonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 76a), the title compound is obtained by reacting 2.20 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-dimethylaminosulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 40 ml of trifluoroacetic acid in 0.90 ml of anisole and 4 ml of methylene chloride and subsequently treating the trifluoroacetate salt with 1N sodium hydroxide solution. M.p. from 183° with decomposition. $R_f$: approximately 0.63 (silica gel, UV 366, n-butanol/pyridine/glacial acetic acid/water 42:24:4:30).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-dimethylaminosulphonyl-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 128b), the title compound is obtained by reacting 4.0 g of 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester with 1.80 ml of N,N-dimethylamidosulphonic acid chloride in a mixture of 100 ml of dioxan and 2 ml of N-methylmorpholine. The crude product is purified by chromatography over 30 times the amount of silica gel. Eluant: methylene chloride with 15% methyl acetate. $R_f$: approximately 0.64 (silica gel, UV 366, double spot diastereoisomeric mixture, toluene/ethyl acetate 1:2).

**Example 133**

**a) The disodium salt of 3-(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

1.5 g of the disodium salt of 3-(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-chloroacetamidothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (for preparation see Example 133b)) are stirred with 0.7 g of thiourea in 15 ml of water for 8 hours at room temperature under a nitrogen atmosphere, the pH of the reaction mixture being maintained constant at 6.8 by the addition of 0.1N aqueous NaOH using a titrator. The mixture is then extracted with ethyl acetate and subsequently washed twice with water. The combined aqueous phases are concentrated *in vacuo* and chromatographed over 150 g of Opti-UPC 12 silica gel. The product-containing fractions eluted with a $H_2O/CH_3CN$ mixture (9:1) are combined, concentrated, and the hydrate of the title compound is precipitated by the addition of ethanol, filtered with suction and dried; IR: 3700—2500 (broad), 1765, 1685, 1640 (shoulder), 1600, 1550 (shoulder), 1500 (Nujol).

**b) The disodium salt of 3-(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-chloroacetamidothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

0.102 ml of triethylamine is added to 200 mg of (2R,S)-2-(2-chloroacetamidothiazol-4-yl)-2-

methanesulphonylaminoacetic acid in 1.82 ml of methylene chloride. The mixture is cooled to 0°, 128 mg of phosphorus pentachloride are added and the whole is stirred for 5 minutes at 0° and for 20 minutes at room temperature. The reaction mixture is then concentrated by evaporation *in vacuo*, digested twice with hexane and then dissolved in 1.8 ml of tetrahydrofuran. The triethylamine hydrochloride which is precipitated is then filtered off. The resulting solution, containing (2R,S)-2-(2-chloroacetamidothiazol-4-yl)-2-methanesulphonylaminoacetic acid chloride, is used directly for the subsequent acylation. 150 mg of 3-(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-ylthiomethyl)-7β-amino-3-cephem-4-carboxylic acid are heated for 1 hour in a reflux condenser with 0.4 ml of N,O-bis(trimethylsilyl)acetamide in 1.5 ml of tetrahydrofuran. The mixture is then cooled to 20°, 0.033 ml of pyridine and the acid chloride solution obtainable in accordance with the above directions are added, and the whole is stirred for 3 hours at room temperature. 2 ml of water are then added, the pH is adjusted to 7 with 1N NaOH, and the whole is concentrated to dryness by evaporation *in vacuo*. The residue is then chromatographed in water over 20 g of Opti-UPC 12 silica gel. The product-containing fractions eluted with water are combined and concentrated, and the hydrate of the title compound is precipitated by the addition of ethanol, filtered with suction and dried. IR: 3700—2500 (broad), 1760, 1685, 1640 (shoulder), 1600, 1550 (shoulder), 1500 (Nujol).

**Example 134**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 1.2 g of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 134b) are reacted with 2.5 ml of trifluoroacetic acid in 2 ml of $CH_2Cl_2$ and 0.38 ml of anisole, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; IR: 3650—2500 (broad), 1775 (shoulder), 1744, 1677, 1604, 1520 (Nujol); UV: 253 (10200; $H_2O$).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 10.2 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetic acid obtainable according to Example 134c) are reacted with 10.9 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 100 ml of tetrahydrofuran (3.3 g of hydroxybenzotriazole; 3×1.73 g of dicyclohexyl carbodiimide in 6.66 ml of tetrahydrofuran each time), worked up and chromatographed. The title compound is obtained; IR: 3400, 3300, 1787, 1740, 1725, 1695, 1630, 1540, 1495 (Nujol).

**c) (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetic acid**

Analogously to Example 6c), 6.8 g of (2R,S)-2-(2-BOC-aminothiazol-4-yl)-glycine are reacted in 60 ml of tetrahydrofuran with 5.2 g of methoxycarbonylmethanesulphonyl chloride (20 ml of N,O-bis(trimethylsilyl)acetamide; 2 ml of pyridine) and worked up. The title compound is obtained and is further processed, without being characterised, in accordance with Example 134b).

**Example 135**

**7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-pivaloyloxymethoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 1.3 g of the disodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-carboxymethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (for preparation see Example 137) and 1.3 ml of iodomethyl pivalate are reacted in 13 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 160° (with decomposition); $[\alpha]_D^{20°}=+29°\pm1°$ (0.92% in DMSO); IR: 3650—2300 (broad), 1785 (shoulder), 1755, 1695, 1650 (shoulder), 1630, 1530 (Nujol); UV: 260 (9000; $CH_3OH$).

**Example 136**

**7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester hydrochloride**

Analogously to Example 70a), 1.0 g of the sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (for preparation see Example 138a)) and 0.52 ml of iodomethyl pivalate are reacted in 10 ml of dimethylformamide, worked up and converted into the hydrochloride. The title compound is obtained; m.p. above 95° (with decomposition); $[\alpha]_D^{20°}=+56°\pm1°$ (0.99% in DMSO); IR: 3660—2300 (broad), 1785, 1747, 1695, 1630, 1540 (Nujol); UV: 255 (9500; $CH_3OH$).

**Example 137**

**The disodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-carboxymethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

2.7 g of the sodium salt of [(2R,S)-2-(2-aminothiazol-4-yl)-2-methoxycarbonylmethane-

sulphonylaminoacetamido]-3-cephem-4-carboxylic acid (for preparation see Example 138a)) are stirred in 135 ml of water with 135 ml of 0.1N aqueous NaOH for 20 minutes at room temperature. The pH is then adjusted to 7 with 2N hydrochloric acid, and the whole is concentrated *in vacuo* and chromatographed as described in Example 1a). The hydrate of the title compound is obtained; m.p. above 220° (with decomposition); $[\alpha]_D^{20°}=+61°\pm1°$ (1.13% in $H_2O$); IR: 3700—2500 (broad), 1780 (shoulder), 1760, 1670 (shoulder), 1630—1565 (broad), 1520 (Nujol); UV: 253 (7000; $H_2O$).

**Example 138**

**a) The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 12 g of the 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 138b) are reacted in 20 ml of $CH_2Cl_2$ and 3.8 ml of anisole with 25 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p.: above 190° (with decomposition); $[\alpha]_D^{20°}=+98°\pm1°$ (0.99% in $H_2O$); IR: 3650—2500 (broad), 1775 (shoulder), 1745, 1678, 1605, 1520 (Nujol); UV: 252 (9800; $H_2O$).

**b) 7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 10.2 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetic acid obtainable according to Example 134c) are reacted with 7.3 g of 7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 100 ml of tetrahydrofuran (3.3 g of hydroxybenzotriazole; 3×1.73 g of dicyclohexyl carbodiimide in 6.66 ml of tetrahydrofuran each time), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=+16°\pm1°$ (1.10% in EtOH); IR: 3400, 3300, 1789, 1740 (shoulder), 1725, 1696, 1635, 1542, 1497 ($CH_2Cl_2$); UV: 258 (14200; EtOH).

**Example 139**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 12a), 2.2 g (2.9 mmol) of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 4.4 ml of $CH_2Cl_2$ and 1.5 ml of anisole with 21 ml of trifluoroacetic acid, worked up, chromatographed and lyophilised. The title compound having an $R_f$ value of 0.55 (silica gel Opti-UPC 12, water:acetonitrile 6:1) is obtained; IR (Nujol): characteristic absorption bands at 3310, 1755, 1617, 1158.

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 12b), 1.8 g (5.0 mmol) of (2R,S)-2-(5-BOC-amino-1,2,4-thiadiazol-3-yl)-2-methanesulphonylaminoacetic acid and 2.2 g (5.0 mmol) of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester are reacted in 40 ml of tetrahydrofuran (0.55 g of hydroxybenzotriazole, 1.25 g of N,N'-dicyclohexyl carbodiimide), worked up and reprecipitated from ether. The title compound is obtained; $R_f$ value: 0.50 (silica gel, ethyl acetate); IR (Nujol): characteristic absorption bands at 1765 and 1160.

**Example 140**

The following compounds can be produced in an analogous manner to Examples 1—139:

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1765 (Nujol); UV: 250 (14100; 0.1N HCl).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1766 (Nujol); UV: 251 (15200; 0.1N HCl).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1762 (Nujol); UV: 240 (18600), 270 (22100; 0.1N HCl).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1761 (Nujol); UV: 249 (1400; 0.1N HCl).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1764 (Nujol); UV: 250 (14800, 0.1N HCl).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770, 1748, 1730, 1692, 1610, 1530 (Nujol); UV: 253 (12500; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 252 (13300; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol): UV: 253 (14400; $H_2O$).

3-(1-carboxymethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1765 (Nujol); UV: 252 (12900; $H_2O$).

3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (13000; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV; 241 (19000), 271 (22500; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethane-sulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1765 (Nujol); UV: 252 (14800; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonyl-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1769 (Nujol); UV: 251 (15000; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 252 (14400; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 250 (15000; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 251 (14100; $H_2O$).

3-(1-carboxymethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methane-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 252 (14900; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1769 (Nujol); UV: 251 (15200; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (14200; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 251 (13900; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 252 (15000; $H_2O$).

3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1669 (Nujol); UV: 253 (14000; $H_2O$).

3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethane-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (14200; $H_2O$).

3-(1-carboxymethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethane-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 250 (14500; $H_2O$).

3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethane-sulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (14700; $H_2O$).

3-[1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthiomethyl]-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV; 252 (13900; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 240 (18000), 270 (22000; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1766 (Nujol); UV: 251 (14000; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylamino-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1770 (Nujol); UV: 253 (15200; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 240 (18300), 270 (21900).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 252 (14800; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 252 (14900; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 253 (14700; $H_2O$).

3-(1-carboxymethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 252 (15500; $H_2O$).

3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 253 (15300; $H_2O$).

3-[1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthiomethyl]-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 252 (15400; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol), 270 (21800; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 249 (13200; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 249 (14100; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 249 (14200; $H_2O$).

3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 249 (15200; $H_2O$).

3-(1-carboxymethyl)-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (14700; $H_2O$).

3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1767 (Nujol); UV: 251 (14900; $H_2O$).

3-[1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthiomethyl]-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 252 (15100; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 240 (19100), 270 (22500; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1768 (Nujol); UV: 251 (14400; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-aminothiazol-4-ylacetylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1767 (Nujol); UV: 251 (14600; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-*p*-nitrobenzenesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1767 (Nujol); UV: 251 (14900; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-*p*-nitrobenzenesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (14800; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-*p*-nitrobenzenesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 252 (15200; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-*p*-nitrobenzenesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 240 (18500), 270 (22000; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-*p*-nitrobenzenesulphonylamino-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1769 (Nujol); UV: 252 (14800; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-*p*-nitrobenzenesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1771 (Nujol); UV: 251 (14700; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-butyrylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 241 (17900); 271 (22500; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-

aminothiazol-4-yl)-2-ethoxycarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 240 (18000); 270 (22100; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (14000; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 251 (14100; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 252 (15000; $H_2O$).

3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid: IR: *inter alia* 1771 (Nujol); UV 251 (15100; $H_2O$).

3-(1-carboxymethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 250 (14700; $H_2O$).

3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 251 (15100; $H_2O$).

3-[1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthiomethyl]-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 252 (14800; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 241 (17700), 272 (21800; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1771 (Nujol); UV: 250 (15000; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1771 (Nujol); UV: 252 (14800; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 2260, 1770 (Nujol); UV: 250 (9400; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 2260, 1769 (Nujol); UV: 251 (10100; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 2260, 1771 (Nujol); UV: 250 (9900; $H_2O$).

3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 2260, (Nujol); UV: 250 (9700; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 2260, 1771 (Nujol); UV: 240 (19000), 270 (22000; $H_2O$).

3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 2260, 1770 (Nujol); UV: 251 (9000; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylamino-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 2260, 1769 (Nujol); UV: 250 (10000; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonyl-aminoacetamido]-3-cephem-4-carboxylate; IR: *inter alia* 2260, 1771 (Nujol); UV: 250 (9800; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 250 (14800; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 251 (14900; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 252 (13800; $H_2O$).

3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (13300, $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 240 (17800); 271 (22400; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonyl-amino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1770 (Nujol); UV: 251 (1400; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1768 (Nujol); UV: 249 (16200; $H_2O$).

3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 255 (14200; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-

aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770; UV: 241 (18000), 271 (22000; $H_2O$).

3-carbamoyloxymethyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyclopropylcarbonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 251 (15200; $H_2O$).

3-methyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (14200; $H_2O$).

3-methoxy-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 252 (14100, $H_2O$).

3-chloro-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 252 (15100; $H_2O$).

3-acetoxymethyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 253 (14800; $H_2O$).

3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 253 (14400; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 241 (19000), 272 (21000; $H_2O$).

3-carbamoyloxymethyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 251 (11000; $H_2O$).

3-pyridiniomethyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1776 (Nujol); UV: 250 (12100; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-cyanoacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1771 (Nujol); UV: 253 (16100; $H_2O$).

3-methyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 251 (14200; $H_2O$).

3-methoxy-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 250 (14300; $H_2O$).

3-chloro-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 251 (13900; $H_2O$).

3-acetoxymethyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (14800; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1771 (Nujol); UV: 240 (17700), 270 (20900; $H_2O$).

3-pyridiniomethyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1770 (Nujol); UV: 251 (14800; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1771 (Nujol); UV: 251 (14800; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 2120, 1760 (Nujol); UV: 241 (17300), 271 (22400; $H_2O$).

3-carbamoyloxymethyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-propioloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 2120, 1764 (Nujol); UV: 249 (9900; $H_2O$).

3-methyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 249 (11100; $H_2O$).

3-methoxy-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1767 (Nujol); UV: 248 (12100; $H_2O$).

3-chloro-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 249 (12400; $H_2O$).

3-acetoxymethyl-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1765 (Nujol); UV: 249 (14200; $H_2O$).

3-(1-carboxymethyl-1H-tetrazol-5-ylthiomethyl)-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (14200; $H_2O$).

3-(1-sulphomethyl-1H-tetrazol-5-ylthiomethyl)-7$\beta$-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 249 (9900; $H_2O$).

3-[1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthiomethyl]-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 248 (10300; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 240 (17700), 271 (21900; $H_2O$.

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1770 (Nujol); UV: 249 (14000; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1769 (Nujol); UV: 250 (14300; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (14100; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1765 (Nujol); UV: 251 (13800; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1765 (Nujol); UV: 249 (13900; $H_2O$).

3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1765 (Nujol); UV: 251 (14600; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 241 (16900); 270 (20100; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1768 (Nujol); UV: 250 (14900; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2,4-dinitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylate; IR: *inter alia* 1768 (Nujol); UV: 250 (15200; $H_2O$).

3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-cyanomethanesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (14300; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-cyanomethanesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 240 (19000), 280 (21100; $H_2O$).

3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(2-cyanomethanesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 249 (14800; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (14200; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 250 (14900; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1767 (Nujol); UV: 251 (13900; $H_2O$).

3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 252 (14100; $H_2O$).

3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (14400; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 241 (18900), 280 (22200; $H_2O$).

3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1765 (Nujol); UV: 251 (14000; $H_2O$).

3-pyridiniomethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1766 (Nujol); UV: 252 (14100; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1767 (Nujol); UV: 251 (15000; $H_2O$).

3-methyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-pyridylsulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (13800; $H_2O$).

3-methoxy-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-pyridylsulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 252 (14100; $H_2O$).

3-chloro-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-pyridylsulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (13800; $H_2O$).

3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-pyridylsulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 250 (14800; $H_2O$).

3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-pyridylsulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1769 (Nujol); UV: 251 (15100; $H_2O$).

3-(2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-pyridylsulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 241 (18900); 270 (21500; $H_2O$).

3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-pyridylsulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (13800; $H_2O$).

3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(3-pyridylsulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1768 (Nujol); UV: 251 (13800; $H_2O$).

3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methylcarbamoylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (15200; $H_2O$).

7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-dimethylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 251 (14000; $H_2O$).

3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-acetylmethylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid; IR: *inter alia* 1770 (Nujol); UV: 252 (14300; $H_2O$).

3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-vinylsulphonylaminoacetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester.

The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-dimethylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid.

7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-guanidinoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid.

The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-ureidoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid.

The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-thioureidoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid.

The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(N-(methoxycarbonyliminomethoxycarbonylamino)-methylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid.

The sodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-(4-pyridyl)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid,

and also the R- and S-derivatives, the salts, for example the sodium salts, and the esters that can be cleaved under physiological conditions, for example the pivaloyloxymethyl, 2-propionyloxyethyl, ethoxycarbonyloxyethyl or tert.-butoxycarbonyloxymethyl ester.

**Example 141**

Dry ampoules or phials containing 0.5 g of the sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid are produced as follows:

| | |
|---|---|
| sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid | 0.5 g |
| mannitol | 0.05 g |

A sterile aqueous solution of the sodium salt of 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-aminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid is sealed under aseptic conditions in 5 ml ampoules or phials and examined.

In the same manner the compounds mentioned in the other Examples can be filled into dry ampoules or phials.

**Example 142**

**7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-pivaloyloxymethoxycarbonylmethanesulphonylamino-acetamido]-3-cephem-4-carboxylic acid pivaloyloxymethyl ester**

1.3 g of the disodium salt of 7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-carboxymethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid (for preparation see Example 137) and 1.3 ml of iodomethyl pivalate are, analogously to Example 70a), reacted in 13 ml of dimethylformamide and 5 ml

of methanol, worked up and converted into the hydrochloride. The title compound is obtained; M.p. above 160° (with decomposition); $[\alpha]_D^{20°}=+29°\pm1°$ (0.92% in DMSO); IR: 3650—2400 (broad), 1785 (shoulder), 1755, 1695, 1650 (shoulder), 1630, 1530 (Nujol); UV; 260 (9000; $CH_3OH$).

**Example 143**

**a) The sodium salt of 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

Analogously to Example 1a), 3.4 g of the 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester obtainable according to Example 143b) are reacted in 6 ml of $CH_2Cl_2$ and 0.98 ml of anisole with 10 ml of trifluoroacetic acid, worked up, chromatographed and reprecipitated. The hydrate of the title compound is obtained; m.p. above 210° (with decomposition); $[\alpha]_D^{20°}=158°\pm1°$ (0.89% in $H_2O$); IR: 3650—2500 (broad), 1750, 1710 (shoulder), 1677, 1610, 1520 (Nujol); UV: 258 (12800; $H_2O$).

**b) 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid diphenylmethyl ester**

Analogously to Example 6b), 10.2 g of the (2R,S)-2-(2-BOC-aminothiazol-4-yl)-2-methoxycarbonylmethanesulphonylaminoacetic acid obtainable according to Example 134c) are reacted with 10.9 g of 3-carbamoyloxymethyl-7β-amino-3-cephem-4-carboxylic acid diphenylmethyl ester in 100 ml of tetrahydrofuran (3.3 g of hydroxybenzotriazole; 3×1.74 g of dicyclohexylcarbodiimide in each case in 6.66 ml of tetrahydrofuran), worked up and chromatographed. The title compound is obtained; $[\alpha]_D^{20°}=0°\pm1°$ (0.94% in $CHCl_3$); IR: 3525, 3420, 3400 (shoulder), 3300, 1787, 1730, 1700 (shoulder), 1581, 1542 ($CH_2Cl_2$); UV: 259 (15400; $CHCl_3$).

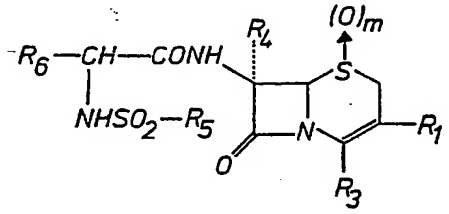
**Example 144**

**The sodium salt of 3-(1,2,3-triazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylamino)-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid**

A slurry of 1.52 g (2.4 mmol) of the sodium salt of 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylamino)-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid and 0.590 g (4.8 mmol) of 5-mercapto-1,2,3-triazole in 7 ml of water is adjusted to pH 7, stirred for 5 hours at 70°, then cooled to 0° and introduced into 300 ml of ethanol. The precipitate formed is filtered off, dissolved in 10 ml of water and purified over 25 g of silylated silica gel (Antec Opti-UPC 12) with water as eluant, yielding the title compound in the form of the dihydrate. M.p. from 131° (with decomposition); $R_f$: approximately 0.75 (silica gel Opti-UPC 12, UV 366, acetonitrile/water 1:4).

**Claims**

1. 7β-acylamido-3-cephem-4-carboxylic acid compounds of the formula




(I),

in which

*m* represents an integer from 0 to 2

$R_1$ represents hydrogen, lower alkyl, lower alkenyl, lower alkoxy, halogen, a group of the formula —$CH_2$—$R_2$ wherein $R_2$ represents a free, esterified or etherified hydroxy or mercapto group or an ammonio group, or a group of the formula —CH=$CHR_2$ wherein $R_2$ represents an etherified mercapto group,

$R_3$ represents carboxy or protected carboxy,

$R_4$ represents hydrogen,

$R_5$ represents an organic radical that is bonded by a carbon atom to the sulphonyl group, and

$R_6$ represents a heterocyclic radical

and stereoisomers, mixtures of these stereoisomers, hydrates and salts of compounds of the formula I.

2. Compounds of the formula I according to claim 1 in which *m* is an integer from 0 to 2, $R_1$ represents hydrogen, lower alkyl, lower alkoxy, halogen, or a group of the formula —$CH_2$—$R_2$ wherein $R_2$ represents lower alkanoyloxy, carbamoyloxy, lower alkylcarbamoyloxy, or aromatic, monocyclic, five- or six-membered heterocyclylthio, or $R_2$ represents an ammonio group, $R_3$ represents carboxy or carboxy that can be cleaved under physiological conditions, $R_4$ represents hydrogen, $R_5$ represents

lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkanoyloxy-lower alkyl, halo-lower alkyl, lower alkylthio-lower alkyl, aminocarboxy-lower alkylthio-lower alkyl, benzoyl-lower alkyl, carboxy-lower alkyl lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, cyano-lower alkyl, sulpho-lower alkyl, sulphamoyl-lower alkyl aminocarboxy-lower alkyl, or a group of the partial formula A in which the group —($C_nH_{2n}$)— represents ethylene or propylene, $R_o$ represents hydrogen or lower alkyl, and R represents hydrogen, lower alkyl, lower alkanoyl, lower alkanoyl substituted by hydroxy, lower alkoxy, halogen carboxy, cyano or by amino, lowar alkenoyl, lower alkynoyl, cycloalkylcarbonyl benzoyl, 4-aminobenzoyl, 4-lower alkanoylaminobenzoyl, 4-cyanobenzoyl, 4-nitrobenzoyl or 2,4-dinitrobenzoyl, pyridylcarbonyl, furoyl, thienyl-carbonyl, hydroxy-pyrimidylcarbonyl, hydroxythiadiazolylcarbonyl, tetrazolyl-lower alkanoyl or aminothiazolyl-lower alkanoyl, the acyl group of a semi-ester of carbonic acid, lower alkanoyloxy substituted carboxy and amino, or benzoyloxycarbonyl, the acyl group of a substituted carbamic acid, or anilinocarbonyl, the acyl group of a substituted thiocarbamic acid, the acyl group of a substituted sulphonic acid, benzenesulphonyl, 4-nitrobenzenesulphonyl, 2,4-dinitrobenzenesulphonyl, aminobenzenesulphonyl, an acylcarbamoyl group, an acylthiocarbamoyl group, 2-oxo-1-imidazolidinocarbonyl, 4-lower alkyl-2,3-dioxo-1-piperazino-carbonyl, or 4-lower alkanesulphonyl-1-piperazinocarbonyl, and $R_6$ represents pyridyl, thienyl, furyl, amino-thiazolyl, hydroxy-pyrimidyl, aminothiadiazolyl hydroxythiadiazolyl, or aminotriazolyl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

3. Compounds of formula I according to claim 2 in which *m* is an integer from 0 to 2, $R_1$ represents hydrogen, methyl, methoxy or ethoxy, chlorine, or a group of formula —$CH_2$—$R_2$ wherein $R_2$ represents acetoxy, carbamoyloxy, lower alkyl carbamoyloxy, or diaza-, triaza-, tetraaza-, thiaza-, thiadiaza-, oxaza- or oxadiaza-cyclythio, which can be substituted by lower alkyl, di-lower alkylamino-lower alkyl, sulpho-lower alkyl, carboxy-lower alkyl, amino, carboxy-lower alkylamino, carbamoyl, or by tetrazolyl-lower alkyl, or $R_2$ represents 2- lower-alkyl-1-pyrazolio, 2-carboxy-lower alkyl-1-pyrazolio, 3-lower alkyl-1-triazolio, pyridinio, or pyridinio substituted by hydroxy-lower alkyl, carboxy, carboxy-lower alkyl, halogen, or by carbamoyl; $R_3$ represents acyloxy-lower alkoxycarbonyl, or lower alkoxycarbonyl-oxy-lower alkoxy- carbonyl; $R_4$ represents hydrogen; $R_5$ represents methyl or ethyl, hydroxymethyl or 2-hydroxyethyl, methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl, 2-vinyloxyethyl, 2-acetoxyethyl, chloromethyl, 2-chloroethyl, 3-chloropropyl, 4-chlorobutyl or 2-bromoethyl, 2-methylthioethyl or 2-ethylthioethyl, 2-(2-amino-2-carboxyethylthio)-ethyl, benzoylmethyl, carboxymethyl or 2-carboxy-ethyl, ethoxycarbonylmethyl or 2-ethoxycarbonyl ethyl, carbamoylmethyl, cyanomethyl, or 1-cyano- or 2-cyanoethyl, sulphomethyl or 2-sulphoethyl, sulphamoylmethyl or 2-sulphamoylethyl, 2-amino-2-carboxyethyl, or a group of the partial formula A in which the group —($C_nH_{2n}$)— represents ethylene or propylene, $R_o$ represents hydrogen or methyl, and R represents hydrogen, methyl or ethyl, formyl or acetyl, lower alkanoyl substituted by hydroxy, methoxy, bromine, carboxy, cyano or by amino, acryloyl, pripioloyl, cyclopropylcarbonyl, benzoyl, 4-aminobenzoyl, 4-acetylaminobenzoyl, 4-cyanobenzoyl, 4-nitrobenzoyl, or 2,4-dinitrobenzoyl, nicotinoyl or isonicotinoyl, 2-furoyl, 2-thienylcarbonyl, 2,6-dihydroxy-1,3-pyrimid-4-ylcarbonyl, 4-hydroxy-1,2,5-thiadiazol-3-ylcarbonyl, 2-tetrazol-5-yl-acetyl, 2-(2-amino-1,3-thiazol-4-yl)-acetyl, lower alkoxycarbonyl, 2-amino-2-carboxy-ethoxycarbonyl or benzoyloxycarbonyl, lower alkylcarbamoyl or anilino-carbonyl, lower alkyl thiocarbamoyl, lower alkanesulphonyl, benzenesulphonyl, 4-nitrobenzenesulphonyl, 2,4-dinitro-benzenesulphonyl, 4-amino-benzenesulphonyl, benzoylcarbamoyl or furoylcarbamoyl, benzoylthiocarbamoyl or furoylthio-carbamoyl, 2-oxo-1-imidazolidinocarbonyl, 4-ethyl-2,3-dioxo-1-piperazinocarbonyl, or 4-methanesulphonyl-1-piperazinocarbonyl, and $R_6$ represents 3- or 4-pyridyl, 2 or 3-thienyl, 2- or 3-furyl, 2-amino-4-thiazolyl, 2,6-dihydroxy-1,3-pyrimid-4-yl, 5-amino-1,2,4-thiadiazol-3-yl, 4-hydroxy-1,2,5-thiadiazol-3-yl or 5 amino-1,2,4-triazol-3-yl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

4. Compounds of formula I according to claim 3 in which *m* is an integer from 0 to 2, $R_1$ represents hydrogen, methyl, methoxy or ethoxy, chlorine, or a group of formula —$CH_2$—$R_2$ wherein $R_2$ represents acetoxy, carbamoyloxy, lower alkylcarbamoyloxy, or imidazolylthio, triazolylthio, tetrazolyl-thio, thiazolythio, thiadiazolylthio, oxazolylthio, oxadiazolylthio or 5,6-dioxotetrahydro-as-triazin-3-yl-thio, which can be substituted by methyl, dimethylaminomethyl, or 2-dimethylaminoethyl, sulpho-methyl or sulphoethyl, carboxymethyl, 2-carboxyethylamino, tetrazol-1H-5-ylmethyl, or $R_2$ represents 2-methyl-1-pyrazolio, 2-carboxymethyl-1-pyrazolio, 3-methyl-1-triazolio, pyridinio or pyridinio substituted by hydroxymethyl, carboxy, carboxymethyl, chlorine or bromine, 3-or 4-hydroxymethyl-pyridinio, 4-carboxypyridinio, 3- or 4-carboxymethylpyridinio, 3- or 4-chloropyridinio, 3- or 4-bromo-pyridinio or 3- or 4-carbamoylpyridinio; $R_3$ represents carboxy or lower alkanoyloxy-lower alkoxy-carbonyl or 1-ethoxycarbonyloxyethoxy-carbonyl or tert-butoxycarbonyloxymethoxycarbonyl, $R_4$ represents hydrogen, $R_5$ represents methyl or ethyl, hydroxymethyl or 2-hydroxyethyl, methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl, 2-vinyloxyethyl, 2-acetoxyethyl, chloromethyl, 2-chloroethyl, 3-chloropropyl, 4-chlorobutyl or 2-bromoethyl, 2-methylthioethyl or 2-ethylthioethyl, 2-(2-amino-2-carboxyethylthio) ethyl, benzoylmethyl, carboxymethyl or 2-carboxyethyl, ethoxycarbonylmethyl or 2-ethoxycarbonylethyl, carbamoylmethyl, cyanomethyl or 1-cyano- or 2-cyanoethyl, sulphomethyl or 2-sulphoethyl, sulphamoylmethyl or 2-sulphamoylethyl, 2-amino-2-carboxyethyl or a group of the

partial formula A in which group —($C_nH_{2n}$)— represents ethylene or propylene, $R_o$ represents hydrogen or methyl, and R represents hydrogen, methyl or ethyl, formyl or acetyl, -hydroxypripionyl, methoxyacetyl, bromoacetyl, carboxyacetyl, cyanoacetyl, or glycyl, acryloyl, pripiolyl, cyclopropylcarbonyl, benzoyl, 4-aminobenzoyl, 4-acetylaminobenzoyl, 4-cyanobenzoyl, 4-nitrobenzoyl, or 2,4-dinitrobenzoyl, nicotinoyl or isonicotinoyl, 2-furoyl, 2-thienylcarbonyl, 2,6-dihydroxy-1,3-pyrimid-4-ylcarboxyl, 4-hydroxy-1,2,5-thiadiazol-3-ylcarbonyl, 2-tetrazol-5-ylacetyl, 2-(2-amino-1,3-thiazol-4-yl)-acetyl, methoxycarbonyl or isopropoxycarbonyl, 2-amino-2-carboxyethoxycarbonyl, benzoyloxycarbonyl, methylcarbamoyl or anilinocarbonyl, methylthiocarbamoyl, methanesulphonyl, benzenesulphonyl, 4-nitrobenzenesulphonyl, 2,4-dinitrobenzenesulphonyl, 4-aminobenzenesulphonyl, benzoylcarbamoyl or furoylcarbamoyl, benzoylthiocarbamoyl or furoylthiocarbamoyl, 2-oxo-1-imidazolidinocarbonyl, 4-ethyl-2,3-dioxo-1-piperazinocarbonyl, or 4-methanesulphonyl-1-piperazinocarbonyl; and $R_6$ is as defined in claim 3, and stereoisomers, mixture of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

5. Compounds of formula I according to claim 4 in which *m* is an integer from 0 to 2, $R_1$ represents hydrogen, methyl, methoxy or ethoxy, chlorine, a group of the formula —$CH_2$—$R_2$ wherein $R_2$ represents acetoxy, carbamoyloxy, lower alkylcarbamoyloxy, or 1H-1,2,3-tetrazol-5-ylthio. 1H-tetrazol-5-ylthio, 1,3,4-thiadiazol-5-ylthio, 5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio, or 5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio which can be substituted by methyl, dimethylaminomethyl or 2-dimethyl aminoethyl, sulphomethyl or sulphoethyl, carboxymethyl, 2-carboxyethylamino, or tetrazol-1H-5-ylmethyl, or $R_2$ is 2-methyl-1-pyrazolio, 2-carboxymethyl-1-pyrazolio, 3-methyl-1-triazolio, hydroxymethyl, carboxymethyl, chlorine or bromine, 3- or 4-hydroxymethylpyridinio, 4-carboxypyridinio, 3- or 4-carboxymethylpyridinio, 3- or 4-chloropyridinio, 3- or 4-bromopyridinio or 3- or 4-carbamoylpyridinio; $R_3$ represents carboxy, lower alkanoyloxymethoxy carbonyl or lower alkanoyloxyethoxycarbonyl, 1-ethoxycarbonyloxyethoxy carbonyl or tert-butoxycarbonyloxymethoxycarbonyl, and $R_4$, $R_5$ and $R_6$ are as defined in claim 4, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

6. Compounds of formula I according to claim 5 in which m $R_1$, $R_4$, $R_5$ and $R_6$ are as defined in claim 5 and $R_3$ is carboxy or pivaloyloxy methoxy carbonyl or 2-propionyloxyethoxycarbonyl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

7. Compounds of the formula I according to claim 1 in which *m* is 0, $R_1$ represents hydrogen, lower alkyl, lower alkoxy, halogen, or a group —$CH_2$—$R_2$— wherein $R_2$ represents lower alkanoyloxy, carbamoyloxy, triazolylthio, tetrazolylthio, tetrazolylthio substituted by lower alkyl, di-lower alkylamino-lower alkyl, sulpho-lower alkyl, carboxy-lower alkyl, or by carbamoyl, thiadiazolylthio, thiadiazolylthio substituted by lower alkyl, 5,6-dioxotetrahydro-as-triazin-3-ylthio substituted by lower alkyl, pyridinio or pyridinio substituted by hydroxy-lower alkyl carboxy, carboxy-lower alkyl, halogen, or by carbamoyl $R_3$ represents carboxy or carboxy that can be cleaved under physiological conditions, $R_4$ represents hydrogen, $R_5$ represents lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, lower alkenyloxy-lower alkyl, halo-lower alkyl, lower alkylthio-lower alkyl, carboxy-lower alkyl, carbamoyl-lower alkyl, cyano-lower alkyl, or a group of the partial formula A that represents 2-aminoethyl, 2-lower alkylaminoethyl, 2-di-lower alkylaminoethyl, 2-sulphoamino-ethyl, lower alkanoylaminoethyl, 2-lower alkoxy-lower alkanoylaminoethyl, 2-halo-lower alkanoylaminoethyl, 2- (-hydroxypropionylamino)-ethyl 2-glycylaminoethyl,2-(3-amino-3-carboxypropionylamino)-ethyl, 2-acryloylaminoethyl, 2-propioloylaminoethyl, 2-cyclopropylcarbonylaminoethyl, 2-benzoylaminoethyl, 2-(4-aminobenzoylamino)-ethyl, 2-(4-acetylaminobenzoylamino)-ethyl, 2-(4-cyano-benzoylamino)-ethyl, 2-(4-nitrobenzoylamino)-ethyl, 2-(3,4-dinitrobenzoylamino)-ethyl, 2-mandeloylaminoethyl, 2-phenylglycylaminoethyl, 2-nicotinoylaminoethyl, 2-isonicotinoylaminoethyl, 2-(2-furoylamino)-ethyl, 2-(2-thienylcarbonylamino)-ethyl, 2-(2,6-dihydroxy-1,3-pyrimid-4-ylcarbonylamino)-ethyl, 2-(4-hydroxy-1,2,5-thiadiazol-3-ylcarbonylamino)-ethyl, 2-(2-tetrazol-1-ylacetylamino)-ethyl, 2-[2-(2-amino-1,3-thiazol-4-yl)-acetylamino]-ethyl, 2-loweralkoxycarbonyl aminoethyl, 2-(2-amino-2-carboxyethoxycarbonylamino)-ethyl, 2-benzoyloxycarbonylaminoethyl, 2-lower alkylcarbamoylaminoethyl, 2-anilinocarbonylaminoethyl, 2-lower alkylthiocarbamoylaminoethyl, 2-lower alkanesulphonylaminoethyl, 2-halomethanesulphonylaminoethyl, 2-cyanomethanesulphonyl aminoethyl, 2-benzenesulphonyl-aminoethyl, 2-(4-nitrobenzenesulphonylamino)-ethyl, 2-(2,4-dinitrobenzenesulphonylamino)-ethyl, 2-benzoylcarbamoylaminoethyl, 2-(2-furoylcarbamoylamino)-ethyl, 2-(2-oxo-1-imidazolidinocarbonylamino)-ethyl, 2-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-ethyl or 2-(4-methanesulphonyl-1-piperazinocarbonyl-amino)-ethyl, and $R_6$ represents aminothiazolyl, aminothiadiazolyl, or aminotriazolyl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

8. Compounds of formula I according to claim 7 in which *m* is 0, $R_1$ is hydrogen, methyl, methoxy, chlorine or a group —$CH_2$—$R_2$ wherein $R_2$ is acetoxy, carbonoyloxy, 1H-1,2,3-triazol-5-ylthio, 1H-tetrazol-5-ylthio, tetrazolthio substituted by methyl, 2-dimethylaminoethyl, sulphomethyl, carboxymethyl, 1-methyl-1H-tetrazol-5-ylthio, 1-sulphomethyl-1H-tetrazol-5-ylthio, 1-carboxymethyl-1H-tetrazol-5-ylthio or 1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthio, 1,3,4-thiadiazol-5-ylthio, thiadiazolylthio substituted by methyl, 5,6-dioxotetrahydro-as-triazin-3-ylthio substituted by methyl, pyridinio,

or pyridinio substituted by hydroxymethyl, carboxy, carboxymethyl, chlorine or bromine, or by carbamoyl, $R_3$ represents carboxy or acyloxy- lower alkoxycarbonyl, or lower alkoxycarbonyloxy-lower alkoxycarbonyl, $R_4$ represents hydrogen, $R_5$ represents methyl or ethyl, hydroxymethyl or hydroxyethyl, methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl, 2-vinyloxyethyl, chloromethyl or 2-chloroethyl, 2-methylthioethyl or 2-ethylthioethyl, carboxymethyl or 2-carboxyethyl, carbamoylmethyl, cyanomethyl or 1-cyano- or 2-cyanoethyl, or a group of the partial formula A that represents 2-aminoethyl, 2-methylaminoethyl or 2-n-hexylaminoethyl, 2-dimethylaminoethyl or 2-di-n-hexylaminoethyl, 2-formylaminoethyl or 2-acetylaminoethyl, 2-methoxyacetylaminoethyl, 2-bromoacetylaminoethyl, 2-methoxycarbonylaminoethyl or 2-isopropoxycarbonylaminoethyl, 2-methylcarbamoylaminoethyl, 2-methylthiocarbamoylaminoethyl, 2-methanesulphonylaminoethyl 2-difluoromethanesulphonylaminoethyl, and $R_6$ represents 2-amino-4-thiazolyl, 5-amino-1,2,4-thiadiazol-3-yl 5-amino-1,2,4-thiadiazol-3-yl, 5-amino-1,2,4-triazol-3-yl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

9. Compounds of formula I according to claim 8 in which *m* is 0, $R_1$ is hydrogen, methyl, methoxy, chlorine, or a group —$CH_2R_2$ wherein $R_2$ represents acetoxy, carbamoyloxy, 1H-1,2,3-triazol-5-ylthio, 1H-tetrazol-5-ylthio, 1-methyl-1H-tetrazol-5-ylthio, 1-sulphomethyl-1H-tetrazol-5-ylthio, 1-carboxymethyl-1H-tetrazol-5-ylthio or 1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthio, 2-methyl-1,3,4-thiadiazol-5-ylthio, 2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio or 4-methyl-5,6-dioxo-1,4,5,6-tetrahydro-as-triazin-3-ylthio, 3- or 4-hydroxymethylpyridinio, 4-carboxypyridinio, 3- or 4-carboxymethyl-pyridinio, 3- or 4-chloropyridinio, 3- or 4-bromopyridinio or 3- or 4-carbamoyl-pyridinio, $R_3$ represents carboxy or lower alkanoyloxy- lower alkoxycarbonyl or 1-ethoxycarbonyloxy-ethoxycarbonyl or tert-butoxycarbonyloxymethoxycarbonyl, and $R_4$, $R_5$ and $R_6$ are as defined in claim 8, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

10. Compounds of formula I according to claim 9 where *m*, $R_1$, $R_4$, $R_5$ and $R_6$ are as defined in claim 9 and $R_3$ is carboxy or lower alkanoyloxymethoxycarbonyl or lower alkanoyloxyethoxycarbonyl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

11. Compounds of formula I according to claim 10 where *m*, $R_1$, $R_4$, $R_5$ and $R_6$ are as defined in claim 10 and $R_3$ is pivaloyloxymethoxycarbonyl or 2-propionyloxyethoxy carbonyl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

12. Compounds of the formula I according to claim 1 in which *m* is 0, $R_1$ represents hydrogen, lower alkoxy, halogen, or a group of the formula —$CH_2$—$R_2$ wherein $R_2$ represents lower alkanoyloxy, carbamoyloxy, tetrazolylthio, tetrazolylthio substituted by lower alkyl, di-lower alkylamino-lower alkyl, sulpho-lower alkyl, or by carboxy-lower alkyl, 5,6-dioxotetrahydro-as-triazin-3-ylthio substituted by lower alkyl, pyridino, or pyridino substituted by hydroxy-lower alkyl, carboxy, carboxy-lower alkyl, halogen, or by carbamoyl $R_3$ represents carboxy, lower alkanoyloxy-lower alkoxycarbonyl or lower alkoxycarbonyloxy-lower alkoxycarbonyl, $R_4$ represents hydrogen, $R_5$ represents lower alkyl, lower alkoxy-lower alkyl, lower alkenyloxy-lower alkyl, halo-lower alkyl, carboxy-lower alkyl, cyano-lower alkyl, or a group of the partial formula A that represents 2-aminoethyl, 2-lower alkyl-aminoethyl, 2-di-lower alkylaminoethyl, 2-sulphoaminoethyl, lower alkanoylaminoethyl, lower alkoxy-lower alkanoylaminoethyl, cyano-lower alkanoylaminoethyl, lower alkanoylaminoethyl, lower alkynoylaminoethyl, cycloalkanoylaminoethyl, 2-(4-hydroxy-1,2,5-thiadiazol-3-ylcarbonylamino)-ethyl, 2-(2-tetrazol-5-ylacetylamino)-ethyl, 2-[2-(2-amino-1,3-thiazol-4-yl)-acetylamino]-ethyl, 2-lower alkoxy-carbonylaminoethyl, 2-lower alkanesulphonylaminoethyl, 2-benzene-sulphonylaminoethyl, 2-benzene-sulphonylaminoethyl wherein benzene is substituted by nitro or amino, 2-(2-oxo-1-imidazolidino-carbonylamino)-ethyl, 2-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-ethyl, or 2-(4-methylsulphonyl-1-piperazinocarbonylamino)-ethyl, and $R_6$ represents aminothiazolyl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

13. Compounds of formula I according to claim 12 in which *m* is 0, $R_1$ represents hydrogen, methoxy, chlorine or a group of formula —$CH_2$—$R_2$ wherein $R_2$ represents acetoxy, carbamoyloxy. 1H-tetrazol-5-ylthio, tetrazolylthio substituted by methyl, 2-dimethylaminoethyl, sulphomethyl or carboxymethyl, 5,6-dioxotetrahydro-as-triazin-3-ylthio substituted by methyl, pyridino, or pyridinio substituted by hydroxymethyl, carboxy, carboxymethyl, chlorine or bromine, or by carbamoyl, $R_3$ represents carboxy, lower alkanoyloxy methoxycarbonyl, or lower alkanoyloxyethoxycarbonyl, or 1-ethoxycarbonyloxyethoxycarbonyl or tert-butoxycarbonyloxy methoxycarbonyl, $R_4$ represents hydrogen, $R_5$ represents methyl or ethyl, methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl, 2-vinyloxyethyl, chloromethyl or 2-chloroethyl, carboxymethyl or 2-carboxyethyl cyanomethyl or 1-cyano- or 2-cyanoethyl, or a group of the partial formula A that represents 2-aminoethyl, 2-methylaminoethyl or 2-ethylaminoethyl, 2-dimethylaminoethyl, 2-sulphoaminoethyl, 2-formylaminoethyl or 2-acetylaminoethyl, 2-methoxyacetylaminoethyl, 2-cyanoacetylaminoethyl, 2-acryloylaminoethyl, 2-propionylaminoethyl, 2-cyclopropanoylaminoethyl 2-(4-hydroxy-1,2,5-thiadiazol-3-ylcarbonylamino)-ethyl, 2-(2-tetrazol-5-ylacetylamino)-ethyl, 2-[2-(2-amino-1,3-thiazol-4-yl)-acetylamino]-ethyl, 2-methoxycarbonylaminoethyl, 2-methanesulphonylaminoethyl, 2-benzenesulphonylaminoethyl, 2-(4-nitrobenzenesulphonylamino)-ethyl, 2-(2,4-dinitrobenzenesulphonylamino)-ethyl, 2-(2-oxo-1-imidazolidinocarbonylamino)-

ethyl, 2-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)-ethyl, or 2-(4-methylsulphonyl-1-piperazinocarbonylamino)-ethyl and $R_6$ represents 2-amino-4-thiazolyl, and stereoisomers, mixtures of these stereoisomers, hydrates and pharmaceutically acceptable salts of such compounds.

14. Compounds of formula I according to claim 13 in which *m*, $R_4$, $R_5$ and $R_6$ are as defined in claim 13 and $R_1$ represents hydrogen, methoxy, chlorine or a group of formula $—CH_2—R_2$ wherein $R_2$ represents acetoxy, carbamoyloxy, 1-H-tetrazol-5-ylthio, 1-methyl-1H-tetrazol-5-ylthio, 1-(2-dimethylaminoethyl)-1H-tetrazol-5-ylthio, 1-carboxymethyl-1H-tetrazol-5-yl-thio, 1-sulphomethyl-1H-tetrazol-5-ylthio or 1-carboxymethyl-1H-tetrazol-5-ylthio, 2-methyl-5,6-dioxo-1,2,5,6-tetrahydro-as-triazin-3-ylthio, or 4-methyl-5,6-dioxo-1,4,5,6-tetrahydros-as-triazin-3-ylthio, pyridinio or 3- or 4-hydroxymethylpyridinio, 4-carboxypyridinio, 3- or 4-carboxymethylpyridinio, 3- or 4-chloropyridinio, 3- or 4-bromopyridinio or 3- or 4-carbamoylpyridinio, and $R_3$ represents carboxy, pivaloyloxymethoxycarbonyl or 2-propionyloxyethoxycarbonyl, 1-ethoxycarbonyloxyethoxycarbonyl or tert-butoxycarbonyloxymethoxycarbonyl, and stereoisomers, mixtures of these stereoisomers hydrates and pharmaceutically acceptable salts of such compounds.

15. 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R)-2-(2-aminothiazol-4-yl)-2-(3-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

16. 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid, according to claim 1.

17. 3-(4-carbamoylpyridiniomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid, according to claim 1.

18. 3-acetoxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

19. 3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-cyanomethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid, according to claim 1.

20. 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-formylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

21. 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid, according to claim 1.

22. 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-(4-nitrobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

23. 3-carbamoyloxymethyl-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-(2-methanesulphonylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

24. 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-acryloylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

25. 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-(4-aminobenzenesulphonylamino)-ethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

26. 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-(2-methoxyacetylaminoethanesulphonylamino)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

27. 3-acetoxymethyl-7β-[(2S)-2-(2-(2-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

28. 3-carbamoyloxymethyl-7β-[(2S)-2-(2-(2-aminothiazol-4-ylacetamido)-ethanesulphonylamino)-2-(2-aminothiazol-4-yl)-acetamido]-3-cephem-4-carboxylic acid, according to claim 1.

29. 3-carbamoyloxymethyl-7β-[(2S)-2-(2-aminothiazol-4-yl)-2-ethanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid, according to claim 1.

30. 3-(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-ylthiomethyl)-7β-[(2R,S)-2-(2-aminothiazol-4-yl)-2-methanesulphonylaminoacetamido]-3-cephem-4-carboxylic acid according to claim 1.

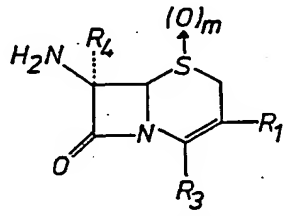
31. The sodium salts of compounds according to claim 1.

32. Pharmaceutically acceptable preparations containing an effective amount of a compound of the formula I according to claim 1 or a pharmaceutically acceptable salt of such a compound having one or more salt-forming groups together with pharmaceutically acceptable carriers.

33. Method of treating infections caused by gram-positive or gram-negative bacteria, which comprises administering to a host a pharmaceutical preparation according to claim 32.

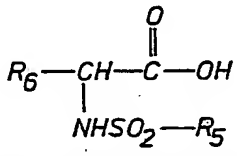
34. Process for the manufacture of 7β-acylamido-3-cephem-4-carboxylic acid compounds of the formula I according to claim 1, in which *m*, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ have the meanings given in claim 1, and stereoisomers, mixtures of these stereoisomers, hydrates and salts of compounds of the formula I, characterised in that

a) in a compound of the formula



(II)

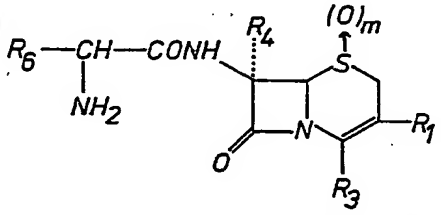
in which $m$, $R_1$, $R_3$ and $R_4$ have the meanings given under formula I and in which a functional group present in $R_1$ is protected and the 7$\beta$-amino group is optionally protected by a group allowing the acylation reaction, the 7$\beta$-amino group is acylated by reaction with an acylating agent that introduces the acyl radical of a carboxylic acid of the formula



(III),

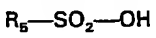
in which $R_5$ and $R_6$ have the meanings given under formula I and in which a functional group present in $R_5$ and/or $R_6$ is in protected form, or

b) in a compound of the formula



(IV)

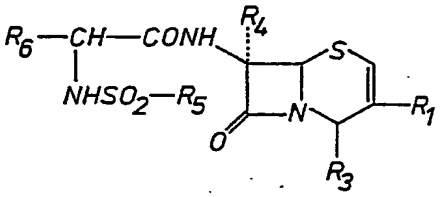
in which $m$, $R_1$, $R_3$, $R_4$ and $R_6$ have the meanings given under formula I and in which a functional group present in $R_1$ and/or $R_6$ is protected and the 2-amino group is optionally protected by a group allowing the sulphonylation reaction, the 2-amino group is sulphonylated by reaction with a sulphonylating agent that introduces the $R_5$ sulphonyl radical of a sulphonic acid of the formula



(V)

in which $R_5$ has the meaning given under formula I and a functional group present in $R_5$ is in protected form, or with a reactive functional acid derivative or a salt thereof, or

c) a 2-cephem compound of the formula



(VI),

in which $R_1$, $R_3$, $R_4$, $R_5$ and $R_6$ have the meanings given under formula I and a functional group present in $R_1$, $R_5$ and/or $R_6$ is optionally in protected form, is isomerised to form the corresponding 3-cephem compound of the formula I, and, if desired, a compound of the formula I obtainable according to the invention is converted into a different compound of the formula I, and/or a compound of the formula I obtainable according to the invention in which $m$ represents 0 is converted into a compound of the formula I in which $m$ represents 1 or 2, and/or a compound of the formula I in which $m$ represents 1 or 2 is converted into a compound of the formula I in which $m$ represents 0, and/or any functional group in a compound of the formula I that is present in protected form is converted into the free functional group, and/or a resulting salt is converted into the free compound or into a different salt, and/or a resulting free compound having a salt-forming group is converted into a salt, and/or a resulting mixture of isomeric compounds of the formula I separated into the individual isomers.

35. Compounds of the formula III as defined in claim 34 in which $R_5$ and $R_6$ have the meanings given in claim 1 under formula I and in which a functional group present in $R_5$ and/or $R_6$ is in free of protected form.

36. Compounds of formula I substantially as described with reference to any of Examples 1 to 140, and 142 to 144.

37. Pharmaceutical preparations according to claim 32 substantially as described with reference to Example 141.

38. Process of producing compounds of formula I according to claim 34 substantially as described with reference to any of Examples 1 to 140 and 142 to 144.

39. Compounds of formula I when produced by a process described in claim 34 or 38.

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